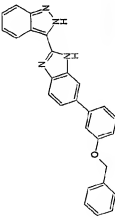
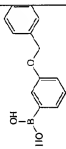
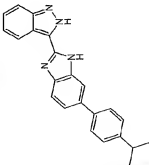
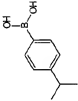
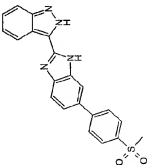
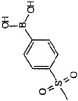
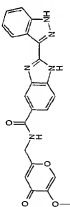
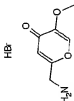
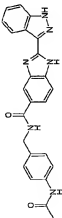

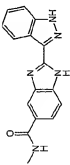

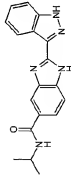

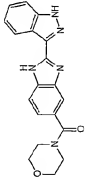

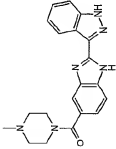

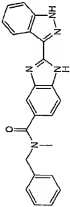

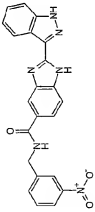
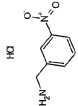
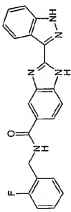

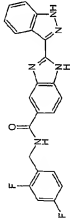

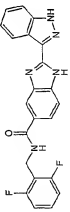

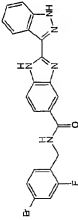

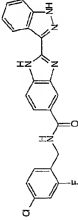

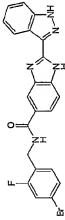
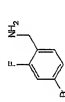
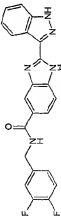
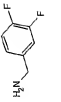


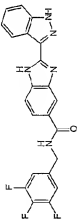

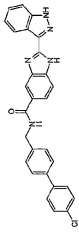
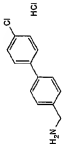
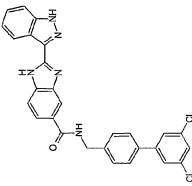
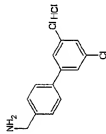
143				C27H20N4O	416.484	417	[M+H] ⁺	3.93	3-[5-(3-Benzoyloxy-phenyl)-1H-benzimidazol-2-yl]-2H-indazole
144				C23H20N4	352.441	353	[M+H] ⁺	3.88	3-[6-(4-Isopropyl-phenyl)-1H-benzimidazol-2-yl]-2H-indazole
145				C21H16N4O2S	388.449	389	[M+H] ⁺	3.03	3-[6-(4-Methanesulfonyl-phenyl)-1H-benzimidazol-2-yl]-2H-indazole

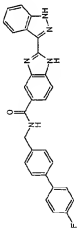
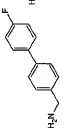
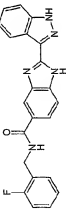

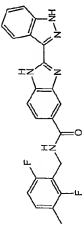

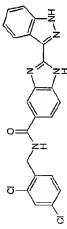
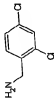
146			C22H17N5O4	415.409	415	[M]	2.31	2-(1H-Indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid (tetrahydro-pyran-4- ylmethyl)-amide
147			C24H20N6O2	424.464	424	[M]	2.58	2-(1H-Indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid 4- acetylamino- benzylamide
148			C16H13N5O	291.314	291	[M]	2.22	2-(1H-Indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid methylamide
149			C18H17N5O	319.368	319	[M]	2.63	2-(1H-Indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid isopropylamide

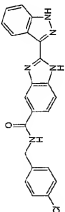

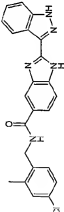

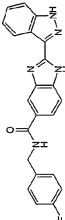

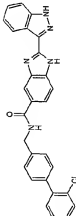
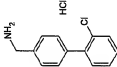
150			C19H17N5O2	347.378	347	[M]	2.23	[2-(1H-Indazol-3-yl)-1H-benzimidazol-5-yl]-morpholin-4-yl-methanone
151			C20H20N6O	360.421	361	[M+H] ⁺	1.94	[2-(1H-Indazol-3-yl)-1H-benzimidazol-5-yl]-[4-methyl-piperazin-1-yl]-methanone
152			C23H19N5O	381.439	381	[M]	3.45	2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzyl-methyl-amide

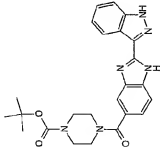
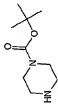
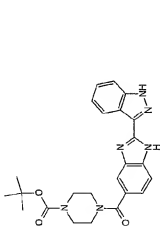
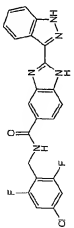
153			C22H16N6O3	412.409	412	[M]	3.32	2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-nitro-benzylamide
154			C22H16FN5O	385.402	385	[M]	2.96	2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-fluoro-benzylamide
155			C22H15F2N5O	403.392	403	[M]	3.26	2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2,4-difluoro-benzylamide
156			C22H15F2N5O	403.392	403	[M]	2.93	2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2,6-difluoro-benzylamide

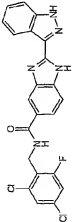

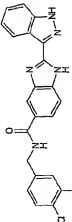

157			C22H15BrFNO	464.303	464	[M]	3.34	2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-bromo-2-fluorobenzyamide
158			C22H15ClFNO	419.847	419	[M]	3.21	2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-chloro-2-fluorobenzyamide
159			C22H15BrFNO	464.303	464	[M]	3.31	2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-bromo-2-fluorobenzyamide
160			C22H15F2NO	403.392	403	[M]	3.64	2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3,4-difluoro-benzyamide

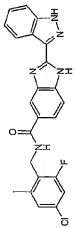

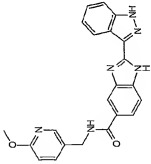
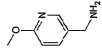
161			C22H14F3N5O	421.382	421	[M]	3.35	2-(1H-indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid 3,4,5-trifluoro- benzylamide
162			C28H20ClN5O	477.955	477	[M]	3.89	2-(1H-indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid (4'- chloro-biphenyl-4- ylmethyl)-amide
163			C28H19Cl2N5O	512.4	512	[M]	4.36	2-(1H-indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid (3,5-dichloro- biphenyl-4-ylmethyl)- amide

164			C28H20FN5O	461.5	461	[M]	3.6	2-(1H-Indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid (4'- fluoro-biphenyl-4- ylmethyl)-amide
165			C22H16FN5O	385.402	385	[M]	2.94	2-(1H-Indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid 2- fluoro-benzylamide
166			C23H17F2N5O	417.419	417	[M]	3.14	2-(1H-Indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid 2,6- difluoro-3-methyl- benzylamide
167			C22H15Cl2N5O	436.302	436	[M]	3.48	2-(1H-Indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid 2,4- dichloro-benzylamide

168			C22H16ClN5O	401.857	401	[M]	3.73	2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-chloro-benzylamide
169			C23H18ClN5O	415.884	415	[M]	3.52	2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-chloro-2-methylbenzylamide
170			C22H16FN5O	385.402	385	[M]	3.09	2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-fluoro-benzylamide
171			C28H20ClN5O	477.955	477	[M]	3.9	2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2'-chloro-biphenyl-4-ylmethyl)-amide

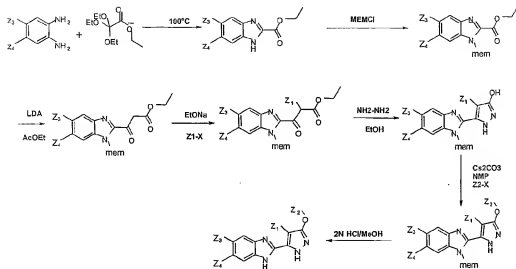
<p>175</p> 				C24H26N6O3	446.511	447	[M+H] ⁺	3.11	4-[2-(1H-indazol-3-yl)-1H-benzimidazole-5-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester
<p>176</p> 						438	[M+H] ⁺		2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,6-difluoro-4-chloro-benzyl)amide

177				437	[M+H] ⁺	2-(1H-Indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid (2,4-dichloro-6- fluoro-benzyl)amide
178				420	[M+H] ⁺	2-(1H-Indazol-3-yl)- 1H-benzimidazole- 5-carboxylic acid (3- fluoro-4-chloro- benzyl)amide

179					434	[M+H] ⁺	2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-fluoro-4-chloro-6-methyl-benzyl)amide
180					399	[M+H] ⁺	2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide

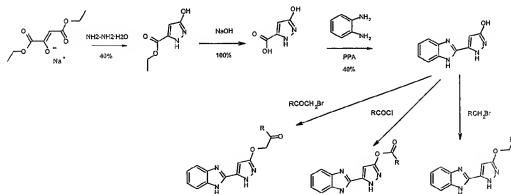
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The products of formula (I) of the present application can also be prepared according to the following process:



- 5 In the above scheme, the values of Z3 and Z4 are chosen from the values of R2 and R3 as defined above and the values of Z1 and -OZ2 are chosen from the values of X1, X2 or X3 with R1 representing a pyrazole radical,

- 10 When Z1, Z3 and Z4 represent a hydrogen atom, it is possible in particular to prepare products of formula (I) of the present application according to the following synthesis scheme:



- 15 Products of formula (I) of the present application which constitute Examples 181 to 228 of the present application are represented in the table 4 hereinbelow: these products can be prepared according to the schemes indicated above and in particular the product of Example 181 can be prepared according to the

-362-

procedure indicated below. The products of Examples 182 to 228 can be prepared like the product of Example 181.

EXAMPLE 181

5 2-[5-(benzyloxy)-2H-pyrazol-3-yl]-1H-benzotriazole

Step 1: the cyclization is performed as in: Chem. Pharm. Bull., 31(4), 1228-1234 (1983); J. Org. Chem., 47(2), 214-221 (1982).

- 10 Step 2: To the crude ester 1.015 g in 50 ml of MeOH, was added 5.5 ml of 6N NaOH and the mixture is heated to reflux during 2 h. After evaporation of most of the methanol, the medium is cooled and conc. HCl is carefully added until pH = 2. After further evaporation to dryness, the solid is triturated three times with 30 ml of MeOH/AcOEt 1/1 and the filtrate evaporated to give 0.875 g of light brown solid after desiccation.
- 15 LC-MS: [gradient acetonitrile/water 0.1% HCOOH; Xterra RP18 2.1 x 50 mm] retention time 0.53 minutes, MH+ = 129, 95% pure

Step 3: To 3.5 g of PPA (polyphosphoric acid) were added 0.701 g of 1,2-phenylenediamine and 0.87 g of the step 2 acid. The mixture is heated to 150°C during 1.5 h. After cooling, conc NH4OH was added

20 until pH = 3. The green precipitate is filtered, washed with water and then with acetone. After one night drying under vacuum at 50°C, 2.1 g of solid remains containing around 50% of mineral salts. MS: EI M+ = 200.

- Step 4: Ex. 181: To 80 mg of the step 3 solid in 4 ml of NMP were added caesium carbonate 137 mg and benzyl bromide 72 mg. After 2 h the mixture is hydrolysed with saturated KH2PO4 and extracted with AcOEt. After evaporation, the crude mixture was submitted to preparative LC-MS to give 8 mg of pure compound:
- 25 LC-MS: [gradient acetonitrile/water 0.1% HCOOH; Xterra RP18 2.1 x 50 mm] retention time 3.17 minutes, MH+ = 291, 97% pure

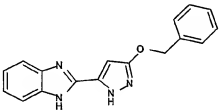
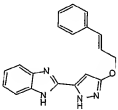
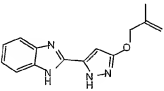
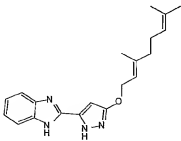
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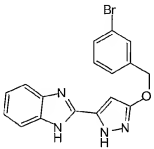
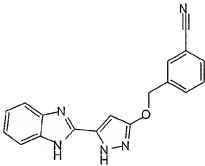
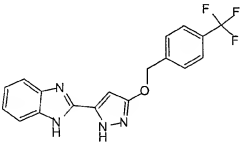
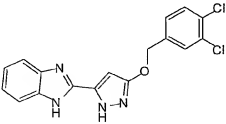
In the same way, the step 4 is carried out with 15 benzyl or allyl bromides, 15 α -bromocarbonyl compounds and 15 acid chlorides in either DMF or NMP to give the expected compounds of TABLE 4. Examples 181 to 228 of the present application are represented in TABLE 4.

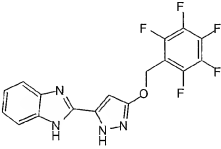
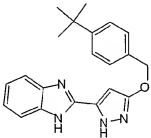
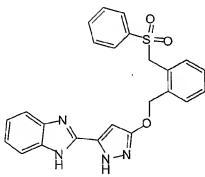
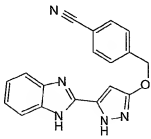
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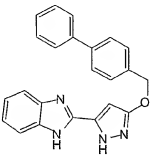
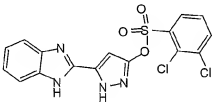
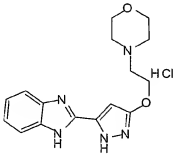
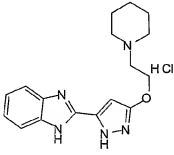
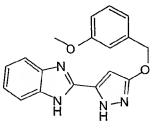
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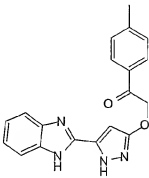
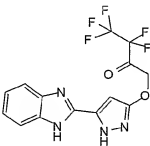
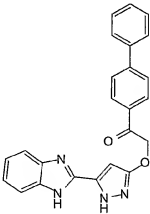
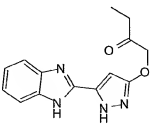
TABLE 4

CHEMISTRY		
	181	2-[5-(benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole
	182	2-[5-(3-Phenyl-allyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole
	183	2-[5-(2-Methyl-allyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole
	184	2-[5-(3,7-Dimethyl-octa-2,6-dienyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole

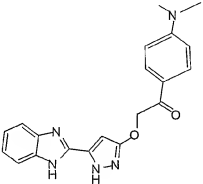
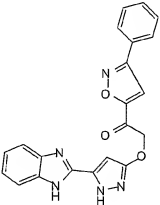
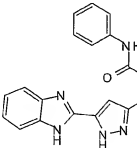
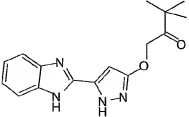
	185	2-[5-(3-Bromo-benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole
	186	3-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxymethyl]-benzonitrile
	187	2-[5-(4-Trifluoromethyl-benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole
	188	2-[5-(3,4-Dichloro-benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole

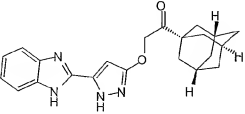
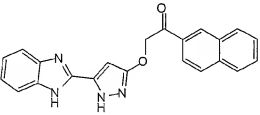
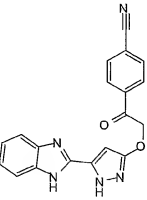
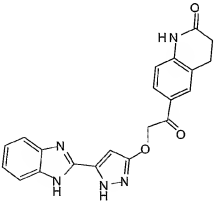
	189	2-(5-Pentafluorophenylmethoxy)-2H-pyrazol-3-yl)-1H-benzimidazole
	190	2-[5-(4-tert-Butylbenzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole
	191	2-[5-(2-Benzenesulfonylmethylbenzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole
	192	4-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxymethyl]-benzonitrile

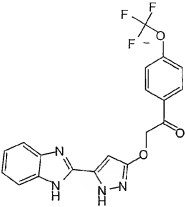
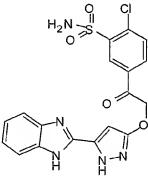
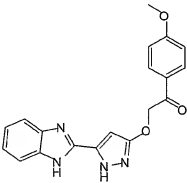
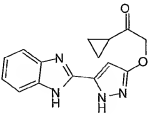
	193	2-[5-(Biphenyl-4-ylmethoxy)-2H-pyrazol-3-yl]-1H-benzimidazole
	194	2,3-Dichlorobenzenesulfonic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester
	195	2-[5-(2-Morpholin-4-ylethoxy)-2H-pyrazol-3-yl]-1H-benzimidazole
	196	2-[5-(2-Piperidin-1-ylethoxy)-2H-pyrazol-3-yl]-1H-benzimidazole
	197	2-[5-(3-Methoxybenzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole

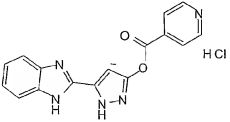
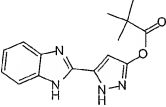
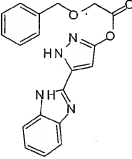
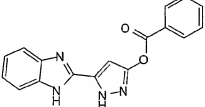
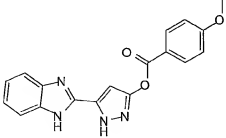
	198	2-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxy] 1-p-tolyl-ethanone
	199	1-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxy] 3,3,4,4,4-pentafluorobutan-2-one
	200	2-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxy] 1-biphenyl-4-yl-ethanone
	201	1-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxy] butan-2-one

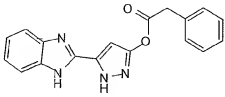
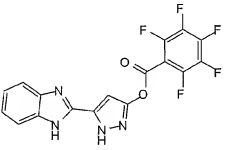
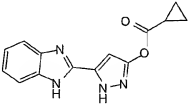
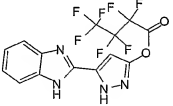
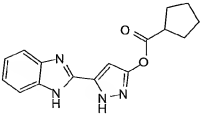
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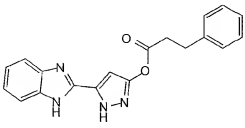
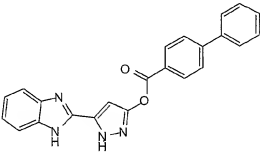
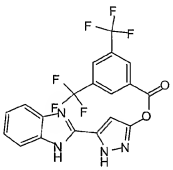
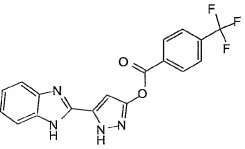
	202	2-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxy] 1-(4-dimethylamino-phenyl)-ethanone
	203	2-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxy] 1-(3-phenyl-isoxazol-5-yl)-ethanone
	204	2-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxy] N-phenyl-acetamide
	205	1-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxy] 3,3-dimethyl-butan-2-one

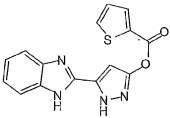
	206	1-Adamantan-1-yl-2-[5-(1H-benzoimidazol-2-yl)-1H-pyrazol-3-yloxy]ethanone
	207	2-[5-(1H-Benzoimidazol-2-yl)-1H-pyrazol-3-yloxy]1-naphthalen-2-yl-ethanone
	208	4-{2-[5-(1H-Benzoimidazol-2-yl)-1H-pyrazol-3-yloxy]-acetyl}-benzonitrile
	209	6-{2-[5-(1H-Benzoimidazol-2-yl)-1H-pyrazol-3-yloxy]-acetyl}-3,4-dihydro-1H-quinolin-2-one

	210	2-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-1-(4-trifluoromethoxy-phenyl)-ethanone
	211	5-[2-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-2-chloro-benzenesulfonamide
	212	2-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-1-(4-methoxy-phenyl)-ethanone
	213	2-[5-(1H-Benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-1-cyclopropyl-ethanone

	214	Isonicotinic acid 5-(1H-benzoimidazol-2-yl)-1H-pyrazol-3-yl ester
	215	2,2-Dimethyl-propionic acid 5-(1H-benzoimidazol-2-yl)-1H-pyrazol-3-yl ester
	216	Benzyloxy-acetic acid 5-(1H-benzoimidazol-2-yl)-1H-pyrazol-3-yl ester
	217	Benzoic acid 5-(1H-benzoimidazol-2-yl)-1H-pyrazol-3-yl ester
	218	4-Methoxy-benzoic acid 5-(1H-benzoimidazol-2-yl)-1H-pyrazol-3-yl ester

	219	Phenyl-acetic acid 5-(1H-benzoimidazol-2-yl)-1H-pyrazol-3-yl ester
	220	2,3,4,5,6-Pentafluorobenzoic acid 5-(1H-benzoimidazol-2-yl)-1H-pyrazol-3-yl ester
	221	Cyclopropanecarboxylic acid 5-(1H-benzoimidazol-2-yl)-1H-pyrazol-3-yl ester
	222	2,2,3,3,4,4,4-Heptafluorobutyric acid 5-(1H-benzoimidazol-2-yl)-1H-pyrazol-3-yl ester
	223	Cyclopentanecarboxylic acid 5-(1H-benzoimidazol-2-yl)-1H-pyrazol-3-yl ester

	224	3-Phenyl-propionic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester
	225	Biphenyl-4-carboxylic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester
	226	3,5-Bis-trifluoromethyl- benzoic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester
	227	4-Trifluoromethyl- benzoic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester

	228	Thiophene-2-carboxylic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester
---	-----	--

5 Example 229: pharmaceutical composition

Tablets corresponding to the formula below were prepared:

Product of Example 1 0.2 g

Excipient for a finished tablet containing..... 1 g

(details of the excipient: lactose, talc, starch,

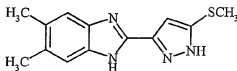
10 magnesium stearate).

Example 1 is taken as pharmaceutical preparation example, it being possible for this preparation to be produced, if desired, with other products in examples in the present application.

15

EXAMPLE 230

(a) 5,6-Dimethyl-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1H-benzimidazole



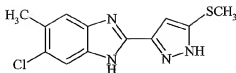
A mixture of 5,6-dimethyl-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole [90mg, Reference Example 1(a)], hydrochloric acid (2mL, 4N) and ethanol (4mL)

20 was heated at reflux temperature for 16 hours then cooled to room temperature. The pH of the reaction mixture was adjusted to 7 by addition of saturated sodium bicarbonate solution. The resulting solid was filtered, then washed with water and then dried in a vacuum oven to give 5,6-dimethyl-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1H-benzimidazole (38mg). LC-MS (METHOD A): $R_T = 2.22$ minutes; 259 (M+H)⁺.

25

(b) 6-Chloro-5-methyl-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1H-benzimidazole

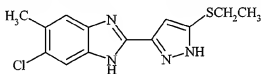
-375-



By proceeding in a similar manner to Example 230(a) above but using 6-chloro-5-methyl-2-(5-methylsulfanyl-1H-pyrazol-3-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole [Reference Example 1(b)] there was prepared 6-chloro-5-methyl-2-(5-methylsulfanyl-1H-pyrazol-3-yl)-1H-

5 benzimidazole.

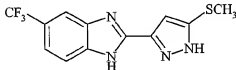
(c) 6-Chloro-2-(5-ethylsulfanyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole



By proceeding in a similar manner to Example 230(a) above but using 6-chloro-2-(5-ethylsulfanyl-1H-pyrazol-3-yl)-5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole [Reference Example 1(c)] there was prepared 6-chloro-2-(5-ethylsulfanyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole.

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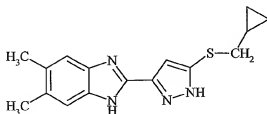
(d) 2-(5-methylsulfanyl-1H-pyrazol-3-yl)-5-trifluoromethyl-1H-benzimidazole



15

By proceeding in a similar manner to Example 230(a) above but using 2-(5-methylsulfanyl-1H-pyrazol-3-yl)-5-trifluoromethyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole [Reference Example 1(d)] there was prepared 2-(5-methylsulfanyl-1H-pyrazol-3-yl)-5-trifluoromethyl-1H-benzimidazole.

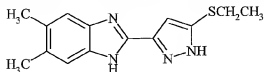
(e) 2-(5-Cyclopropylmethylsulfanyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole



20

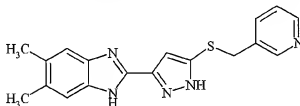
By proceeding in a similar manner to Example 230(a) above but using 2-(5-cyclopropylmethylsulfanyl-1H-pyrazol-3-yl)-5,6-dimethyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole [Reference Example 1(e)] there was prepared 2-(5-cyclopropylmethylsulfanyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole. LC-MS (METHOD A): $R_T = 2.47$ minutes; $299 (M+H)^+$.

- (f) 2-(5-Ethylsulfanyl)-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzotriazole



- By proceeding in a similar manner to Example 230(a) above but using 5,6-dimethyl-2-(5-ethylsulfanyl-
 5 1H-pyrazol-3-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzotriazole [Reference Example 1(f)]
 there was prepared 2-(5-ethylsulfanyl)-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzotriazole. LC-MS
 (METHOD A): $R_T = 2.32$ minutes; 273 (M+H)⁺.

- (g) 5,6-Dimethyl-2-[5-(pyridin-3-ylmethylsulfanyl)-1H-pyrazol-3-yl]-1H-benzotriazole

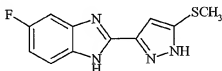


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- By proceeding in a similar manner to Example 230(a) above but using 5,6-dimethyl-2-[5-(pyridin-3-
 yl)methylsulfanyl-1H-pyrazol-3-yl]-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzotriazole
 [Reference Example 1(g)] there was prepared 5,6-dimethyl-2-[5-(pyridin-3-ylmethylsulfanyl)-1H-
 pyrazol-3-yl]-1H-benzotriazole as a colourless solid.

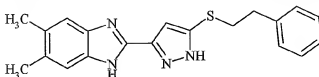
15

- (h) 5-Fluoro-2-[5-methylsulfanyl)-1H-pyrazol-3-yl]-1H-benzotriazole



- By proceeding in a similar manner to Example 230(a) above but using 5-fluoro-2-(5-methylsulfanyl-
 1H-pyrazol-3-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzotriazole [Reference Example 1(h)]
 20 there was prepared 5-fluoro-2-[5-methylsulfanyl)-1H-pyrazol-3-yl]-1H-benzotriazole. MS: 249
 (M+H)⁺.

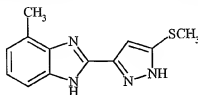
- (i) 5,6-Dimethyl-2-(5-phenethylsulfanyl)-1H-pyrazol-3-yl)-1H-benzotriazole



By proceeding in a similar manner to Example 230(a) above but using 5,6-dimethyl-2-(5-phenethylsulfanyl-1H-pyrazol-3-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-benzimidazole [Reference Example 1(i)] there was prepared 5,6-dimethyl-2-(5-phenethylsulfanyl-1H-pyrazol-3-yl)-1H-benzimidazole.

5

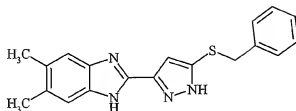
- (j) 4-Methyl-2-(5-methylsulfanyl-1H-pyrazol-3-yl)-1H-benzimidazole



- By proceeding in a similar manner to Example 230(a) above but using 4-methyl-2-(5-methylsulfanyl-1H-pyrazol-3-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-benzimidazole [Reference Example 1(j)] there was prepared 4-methyl-2-(5-methylsulfanyl-1H-pyrazol-3-yl)-1H-benzimidazole. MS: 245 (M+H)⁺.

10

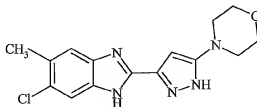
- (k) 5,6-Dimethyl-2-(5-benzylsulfanyl-1H-pyrazol-3-yl)-1H-benzimidazole



- By proceeding in a similar manner to Example 230(a) above but using 2-(5-benzylsulfanyl-1H-pyrazol-3-yl)-5,6-dimethyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-benzimidazole [Reference Example 1(k)] there was prepared 5,6-dimethyl-2-(5-benzylsulfanyl-1H-pyrazol-3-yl)-1H-benzimidazole.

15

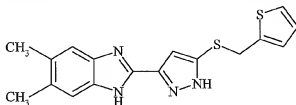
- (l) 6-Chloro-5-methyl-2-(5-morpholin-4-yl-1H-pyrazol-3-yl)-1H-benzimidazole



20

By proceeding in a similar manner to Example 230(a) above but using 6-chloro-5-methyl-2-(5-morpholin-4-yl-1H-pyrazol-3-yl)-1-(2-trimethylsilanyl-ethoxymethyl)-1H-benzimidazole [Reference Example 1(l)] there was prepared 6-chloro-5-methyl-2-(5-morpholin-4-yl-1H-pyrazol-3-yl)-1H-benzimidazole.

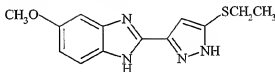
- (m) 5,6-Dimethyl-2-[5-(thiophen-2-ylmethylsulfanyl)-1H-pyrazol-3-yl]-1H-benzoimidazole



- By proceeding in a similar manner to Example 230(a) above but using 5,6-dimethyl-2-[5-(thiophen-2-ylmethylsulfanyl)-1H-pyrazol-3-yl]-1-(2-trimethylsilanyl-ethoxymethyl)-1H-benzoimidazole [Reference Example 1(m)] there was prepared 5,6-dimethyl-2-[5-(thiophen-2-ylmethylsulfanyl)-1H-pyrazol-3-yl]-1H-benzoimidazole.

EXAMPLE 231

- 10 (2-(5-Ethylsulfanyl-1H-pyrazol-3-yl)-5-methoxy-1H-benzoimidazole hydrochloride

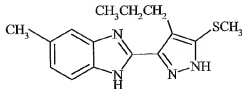


- A mixture of 3,3-bis-ethylsulfanyl-1-[5-methoxy-1-(2-trimethylsilanyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-propanone [~0.78mmole, Reference Example 2(j)] and hydrazine hydrate (500μL) in ethanol (6mL) was heated at reflux temperature for 18 hours, then evaporated. The residue was purified on the Flashmaster to give 2-(5-ethylsulfanyl-1H-pyrazol-3-yl)-5-methoxy-1-(2-trimethylsilanyl-ethoxymethyl)-1H-benzoimidazole which was treated with ethanol (6mL) and hydrochloric acid (3mL). This mixture was heated at reflux temperature for 18 hours and then evaporated to give 2-(5-ethylsulfanyl-1H-pyrazol-3-yl)-5-methoxy-1H-benzoimidazole hydrochloride. LC-MS (METHOD A): $R_T = 2.17$ minutes; 275 (M+H)⁺.

20

EXAMPLE 232

- (a) 5-Methyl-2-(5-methylsulfanyl-4-propyl-1H-pyrazol-3-yl)-1H-benzoimidazole

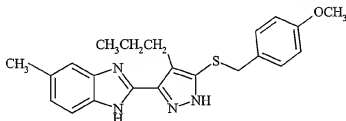


- A mixture of 2-(bis-methylsulfanyl-methylene)-1-(5-methyl-1H-benzoimidazol-2-yl)-pentan-1-one [~0.49mmole, Reference Example 2(i)] and hydrazine hydrate (200μL) in ethanol (6mL) was heated at reflux temperature for 2 days, then evaporated. The mixture was then treated with hydrochloric acid

(4mL, 4N) and heating was continued at reflux temperature for a further 24 hours. The reaction mixture was cooled, then neutralised by addition of sodium hydroxide solution (4N) and then extracted with dichloromethane. The extract was evaporated to give 5-methyl-2-(5-methylsulfanyl-4-propyl-1H-pyrazol-3-yl)-1H-benzoimidazole. MS: 287 (M+H)⁺.

5

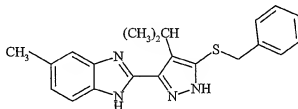
(b) 2-(5-(4-methoxy-benzylsulfanyl)-4-propyl-1H-pyrazol-3-yl)-5-methyl-1H-benzoimidazole



By proceeding in a similar manner to Example 233(a) above but using 2-[bis-(4-methoxy-benzylsulfanyl)-methylene]-1-(5-methyl-1H-benzoimidazol-2-yl)-pentan-1-one [Reference Example 2(m)] there was prepared 2-(5-(4-methoxy-benzylsulfanyl)-4-propyl-1H-pyrazol-3-yl)-5-methyl-1H-benzoimidazole. MS: 393 (M+H)⁺.

10

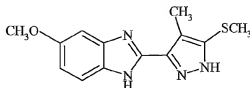
(c) 2-(5-Benzylsulfanyl-4-isopropyl-1H-pyrazol-3-yl)-5-methyl-1H-benzoimidazole



By proceeding in a similar manner to Example 232(a) above but using 2-(bis-benzylsulfanyl-methylene)-3-methyl-1-(5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl)-butan-1-one [Reference Example (2n)] there was prepared 2-(5-benzylsulfanyl-4-isopropyl-1H-pyrazol-3-yl)-5-methyl-1H-benzoimidazole. MS: 363 (M+H)⁺.

20

(d) 2-(5-Methylsulfanyl-4-methyl-1H-pyrazol-3-yl)-5-methoxy-1H-benzoimidazole

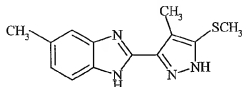


By proceeding in a similar manner to Example 232(a) above but using 1-[5-methoxy-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-2-methyl-3-(bis-methanesulfanyl)-1-

-380-

propenone [Reference Example 2(r)] there was prepared 2-(5-methylsulfonyl-4-methyl-1H-pyrazol-3-yl)-5-methoxy-1H-benzimidazole.

(e) 2-(5-Methylsulfonyl-4-methyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole



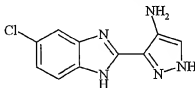
5

By proceeding in a similar manner to Example 232(a) above but using 1-[5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-2-methyl-3-(bis-methanesulfonyl)-1-propenone [Reference Example 2(t)] there was prepared 2-(5-methylsulfonyl-4-methyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole.

10

EXAMPLE 233

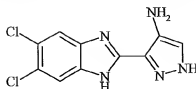
(a) 3-(5-Chloro-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine



A solution of 5-chloro-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole [91 mg, Example 239(a)] in ethanol (40mL), under nitrogen, was treated with palladium on carbon (spatula tip, 5%). The mixture was stirred under hydrogen for 3 hours and then filtered through Celite. The filter pad was washed well with dichloromethane. The combined filtrate and washings were evaporated to give 3-(5-chloro-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine (116mg). LC-MS (METHOD A): $R_T = 2$ minutes; 234 (M+H)⁺.

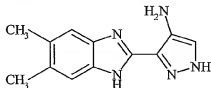
20

(b) 3-(5,6-Dichloro-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine



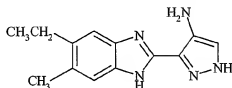
By proceeding in a similar manner to Example 233(a) above but using 5,6-dichloro-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole [Example 239(b)] there was prepared 3-(5,6-dichloro-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine. LC-MS (METHOD A): $R_T = 2.37$ minutes; 268 (M+H)⁺.

25

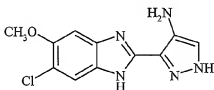
(c) 3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine

By proceeding in a similar manner to Example 233(a) above but using 5,6-dimethyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole [Example 249(a)] there was prepared 3-(5,6-dimethyl-1H-

- 5 benzoimidazol-2-yl)-1H-pyrazol-4-ylamine as a brown solid. LC-MS (METHOD B): $R_T = 2.29$ minutes; 228.25 (M+H)⁺.

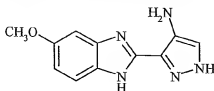
(d) 3-(5-Ethyl-6-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine

- 10 By proceeding in a similar manner to Example 233(a) above but using 5-ethyl-6-methyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole [Example 249(b)] there was prepared 3-(5-ethyl-6-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine as a brown solid. LC-MS (METHOD B): $R_T = 2.14$ minutes; 242.20 (M+H)⁺.

15 (e) 3-(6-chloro-5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine

By proceeding in a similar manner to Example 233(a) above but using 6-chloro-5-methoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole [0.7g, Example 249(c)] there was prepared 3-(6-chloro-5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (0.54 g) as a brown foam. MS 264 (M+H)⁺.

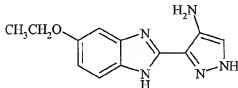
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(f) 3-(5-Methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine

By proceeding in a similar manner to Example 233(a) above but using 5-methoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole [373mg, Example 257(f)] there was prepared 3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine (257mg) as a dark brown solid. LC-MS (Method H): $R_T = 1.23$ minutes, 230.25 (M+H)⁺, 228.25 (M-H)⁻.

5

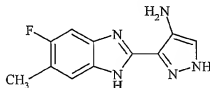
(g) 3-(5-Ethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine



By proceeding in a manner similar to Example 233(a) above but using 5-ethoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole [407mg, Example 252(c)] there was prepared 3-(5-ethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine (375mg) as a dark brown oil. LC-MS (Method H): $R_T = 1.43$ minutes, 244.26 (M+H)⁺, 242.28 (M-H)⁻.

10

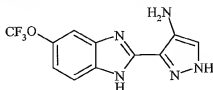
(h) 3-(5-Fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine



By proceeding in a manner similar to Example 233(a) above but using 5-fluoro-6-methyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole [Example 249(d)] there was prepared 3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine (0.590g) as a brown solid. LC-MS (METHOD J): $R_T = 2.25$ minutes, MS: 232.29 (M+H)⁺.

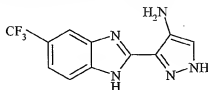
15

20 (i) 3-(5-Trifluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine



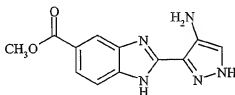
By proceeding in a manner similar to Example 233(a) above but using 5-trifluoromethoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole [Example 249(e)] there was prepared 3-(5-trifluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine (0.920g) as a brown solid. LC-MS (METHOD J): $R_T = 2.76$ minutes, 284.23 (M+H)⁺.

25

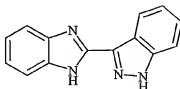
(j) 3-(5-Trifluoromethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine

By proceeding in a manner similar to Example 233(a) above but using 5-trifluoromethyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole [Example 249(f)] there was prepared 3-(5-trifluoromethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (0.150g) as a brown solid. LC-MS (METHOD B): $R_T = 3.00$ minutes, 268.16 (M+H)⁺.

10 (k) 2-(4-Amino-1H-pyrazol-3-yl)-1H-benzoimidazole-5-carboxylic acid methyl ester



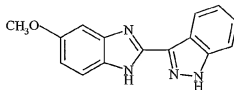
By proceeding in a manner similar to Example 233(a) above but using 2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole-5-carboxylic acid methyl ester [Example 249(h)] there was prepared 2-(4-amino-1H-pyrazol-3-yl)-1H-benzoimidazole-5-carboxylic acid methyl ester (1.10g) as an off-white solid. LC-MS (METHOD B): $R_T = 2.40$ minutes, 258.17 (M+H)⁺.

EXAMPLE 234(a) 3-(1H-Benzoimidazol-2-yl)-1H-indazole

20 A mixture of 1,2-diaminobenzene (108mg), indazole-3-carboxylic acid (118mg) and polyphosphoric acid (1mL) was heated at 150-160°C for 24 hours. The mixture was cooled, then diluted with ice water (10mL) and then treated with ethyl acetate (10mL). The aqueous layer was basified by addition of solid potassium carbonate. The layers were separated and the aqueous layer was extracted with ethyl acetate (10mL). The combined organic phases were dried and then evaporated. The residue was
25 subjected to chromatography on silica eluting with a mixture of heptane and ethyl acetate to give

3-(1H-benzoimidazol-2-yl)-1H-indazole (78mg). LC-MS (METHOD A): R_T = 1.28 minutes; 235 (M+H)⁺.

(b) 3-(5-Methoxy-1H-benzoimidazol-2-yl)-1H-indazole

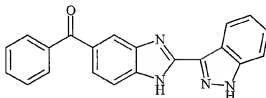


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By proceeding in a similar manner to Example 234(a) above but using 4-methoxy-1,2-diaminobenzene hydrochloride there was prepared 3-(5-methoxy-1H-benzoimidazol-2-yl)-1H-indazole as a solid.

LC-MS (METHOD A): R_T = 1.28 minutes; 265 (M+H)⁺.

10 (c) [2-(indazol-3-yl)-1H-benzoimidazol-5-yl]-phenyl-methanone

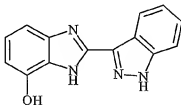


By proceeding in a similar manner to Example 234(a) above but using 3,4-diaminobenzophenone there was prepared [2-(indazol-3-yl)-1H-benzoimidazol-5-yl]-phenyl-methanone as a solid.

LC-MS (METHOD A): R_T = 1.73 minutes; 339 (M+H)⁺.

15

(d) 2-(1H-indazol-3-yl)-3H-benzoimidazol-4-ol

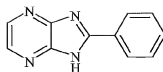


By proceeding in a similar manner to Example 234(a) above but using 2,3-diaminophenol there was prepared 2-(1H-indazol-3-yl)-3H-benzoimidazol-4-ol as a solid. LC-MS (METHOD A): R_T = 1.63

20 minutes; 251 (M+H)⁺.

(e) 2-Phenyl-1H-imidazol[4,5-b]pyrazine

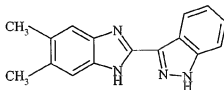
-385-



By proceeding in a similar manner to Example 234(a) above but using 2,3-diaminopyrazine [Reference Example 9] and benzoic acid there was prepared 2-phenyl-1H-imidazo[4,5-b]pyrazine as a pale brown solid, mp 239-240°C. HPLC (METHOD A1): $R_T = 10.18$ minutes.

5

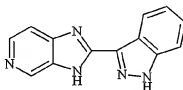
(f) 3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1H-indazole



By proceeding in a similar manner to Example 234(a) above but using 1,2-diamino-4,5-dimethylbenzene there was prepared 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-indazole (28mg).

10 LC-MS (METHOD A): $R_T = 1.34$ minutes; 263 (M+H)⁺.

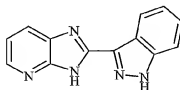
(g) 2-(1H-indazol-3-yl)-3H-imidazo[4,5-c]pyridine



By proceeding in a similar manner to Example 234(a) above but using 3,4-diaminopyridine there was

15 prepared 2-(1H-indazol-3-yl)-3H-imidazo[4,5-c]pyridine as a solid. MS: 236 (M+H)⁺. HPLC (METHOD A): $R_T = 2.48$ minutes.

(h) 2-(1H-indazole-3-yl)-3H-imidazo[4,5-b]pyridine

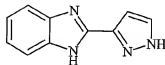


By proceeding in a similar manner to Example 234(a) above but using 2,3-diaminopyridine there was prepared 2-(1H-indazole-3-yl)-3H-imidazo[4,5-b]pyridine as a solid. MS: 236 (M+H)⁺. HPLC (METHOD A): R_T = 2.49 minutes.

5

EXAMPLE 235

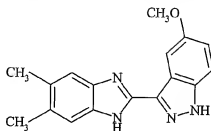
(a) 2-(1H-Pyrazol-3-yl)-1H-benzoimidazole



A mixture of 1H-pyrazole-3-carbaldehyde (0.961g, Reference Example 10), o-phenylenediamine (0.973g), sodium bisulfite (1.898g) and dry dimethylformamide (10mL) was stirred at reflux for 2 hours, then cooled to room temperature and then poured onto cracked ice (35g). The mixture was filtered and the solid was washed with aqueous sodium bicarbonate and then with water. The solid was vacuum dried at 70°C and then recrystallised from ethanol to give 2-(1H-pyrazol-3-yl)-1H-benzoimidazole (0.645g) as a pale yellowish solid, mp 335-338°C. [Elemental analysis: - C, 62.56%, H, 4.04%, N, 29.14%. Calculated for C₁₀H₈N₄: - C, 65.19%, H, 4.39%, N, 30.42%].

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(b) 3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-5-methoxy-1H-indazole

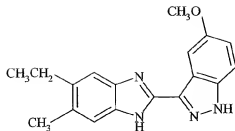


By proceeding in a similar manner to Example 235(a) above but using 3-formyl-5-methoxy-indazole-1-carboxylic acid *tert*-butyl ester [Reference Example 20(a)] and 4,5-dimethylbenzene-1,2-diamine there was prepared 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-5-methoxy-1H-indazole as a white solid. LC-MS (METHOD B): R_T = 2.35 minutes; 289 (M+H)⁺.

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(c) 3-(5-Ethyl-6-methyl-1H-benzoimidazol-2-yl)-5-methoxy-1H-indazole

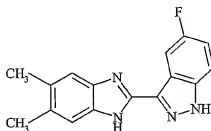
-387-



- By proceeding in a manner similar to Example 235(a) above but using 3-formyl-5-methoxy-indazole-1-carboxylic acid *tert*-butyl ester [Reference Example 20(a)] and 4-ethyl-5-methyl phenylene diamine [Reference Example 30], and subjecting the reaction product to flash column chromatography on silica
 5 eluting with a mixture of ethyl acetate and 40-60 petrol (1:1, v/v), there was prepared, 3-(5-ethyl-6-methyl-1H-benzotriazol-2-yl)-5-methoxy-1H-indazole as a pale yellow solid.

LC-MS (METHOD B): $R_T = 2.48$ minutes; 307 (M+H)⁺.

- (d) 3-(5,6-Dimethyl-1H-benzotriazol-2-yl)-5-fluoro-1H-indazole



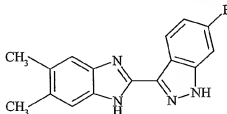
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By proceeding in a manner similar to Example 235(a) above but using 5-fluoro-1H-indazole-3-carbaldehyde [Reference Example 6(c)] and 4,5-dimethylbenzene-1,2-diamine there was prepared 3-(5,6-dimethyl-1H-benzotriazol-2-yl)-5-fluoro-1H-indazole as a brown solid.

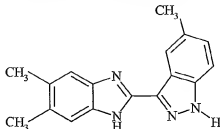
LC-MS (METHOD B): $R_T = 2.41$ minutes; 281 (M+H)⁺.

15

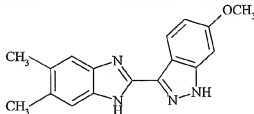
- (e) 3-(5,6-Dimethyl-1H-benzotriazol-2-yl)-6-fluoro-1H-indazole



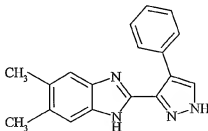
- By proceeding in a manner similar to Example 235(a) above but using 6-fluoro-1H-indazole-3-carbaldehyde [Reference Example 6(d)] and 4,5-dimethylbenzene-1,2-diamine there was prepared
 20 3-(5,6-dimethyl-1H-benzotriazol-2-yl)-6-fluoro-1H-indazole (0.104g) as a brown solid. MS: 281 (M+H)⁺. HPLC (METHOD B1): $R_T = 23.6$ minutes.

(f) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-indazole

- By proceeding in a manner similar to Example 235(a) above but using 5-methyl-1H-indazole-3-carbaldehyde [Reference Example 6(e)] there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-indazole as a brown solid. LC-MS (METHOD B): $R_T = 2.35$ minutes; $277 (M+H)^+$.

(g) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-6-methoxy-1H-indazole

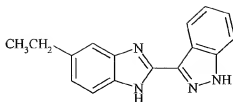
- By proceeding in a manner similar to Example 235(a) above but using 6-methoxy-1H-indazole-3-carbaldehyde [Reference Example 6(f)] there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-methoxy-1H-indazole as a pale orange solid. LC-MS (METHOD B): $R_T = 2.52$ minutes; $293 (M+H)^+$.

(h) 5,6-Dimethyl-2-(4-phenyl-1H-pyrazol-3-yl)-1H-benzimidazole

- By proceeding in a manner similar to Example 235(a) above but using 4-phenyl-1H-pyrazole-3-carbaldehyde [Reference Example 6(g)] there was prepared 5,6-dimethyl-2-(4-phenyl-1H-pyrazol-3-yl)-1H-benzimidazole as a white solid. LC-MS (METHOD B): $R_T = 2.35$ minutes; $289 (M+H)^+$.

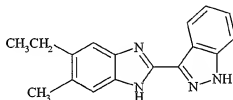
- (i) 3-(5-Ethyl-1H-benzimidazol-2-yl)-1H-indazole

-389-



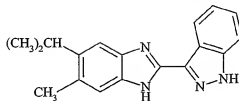
- By proceeding in a manner similar to Example 235(a) above but using 4-ethyl-phenylene diamine [Reference Example 29(a)], a reaction temperature of 160°C and subjecting the reaction product to flash column chromatography on silica eluting with a mixture of ethyl acetate and hexane (2:1) there was prepared 3-(5-ethyl-1H-benzoimidazol-2-yl)-1H-indazole as an off-white solid. LC-MS (Method D): $R_T = 23.13$ minutes, 263.3 (M+H)⁺.

(j) 3-(5-Ethyl-6-methyl-1H-benzoimidazol-2-yl)-1H-indazole



- By proceeding in a manner similar to Example 235(i) above but using 4-ethyl-5-methyl-phenylene diamine [Reference Example 30(a)] there was prepared 3-(5-ethyl-6-methyl-1H-benzoimidazol-2-yl)-1H-indazole as an off-white solid. LC-MS (Method D): $R_T = 23.79$ minutes, 277.3 (M+H)⁺.

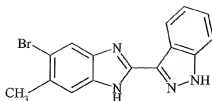
(k) 3-(5-Isopropyl-6-methyl-1H-benzoimidazol-2-yl)-1H-indazole



- By proceeding in a manner similar to Example 235(i) above but using 4-isopropyl-5-methyl-phenylene diamine [Reference Example 30(b)] there was prepared 3-(5-isopropyl-6-methyl-1H-benzoimidazol-2-yl)-1H-indazole as an off-white solid. MS: 291.03 (M+H)⁺. HPLC (METHOD B1): $R_T = 23.39$ minutes.

(l) 3-(5-Bromo-6-methyl-1H-benzoimidazol-2-yl)-1H-indazole

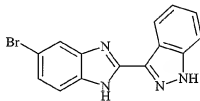
-390-



By proceeding in a manner similar to Example 235(i) above but using 4-bromo-5-methyl-phenylene diamine [Reference Example 30(c)] there was prepared 3-(5-bromo-6-methyl-1H-benzimidazol-2-yl)-1H-indazole as an off-white solid. MS: 329.09 (M+H)⁺. HPLC (METHOD B1): R_T = 22.74 minutes.

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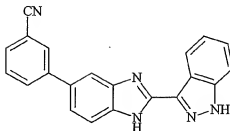
(m) 3-(5-Bromo-1H-benzimidazol-2-yl)-1H-indazole



By proceeding in a manner similar to Example 235(i) above but using 4-bromo-phenylene diamine [Reference Example 30(e)] there was prepared 3-(5-bromo-1H-benzimidazol-2-yl)-1H-indazole as a brown solid. LC-MS (Method D): R_T = 23.46 minutes, 315.15 (M+H)⁺.

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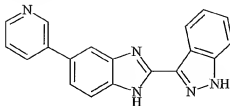
(n) 3-(5-(3-Cyano)phenyl-1H-benzimidazol-2-yl)-1H-indazole



By proceeding in a manner similar to Example 235(i) above but using 3',4'-diaminobiphenyl-3-carbonitrile [Reference Example 30(f)] there was prepared 3-(5-(3-cyano)phenyl-1H-benzimidazol-2-yl)-1H-indazole as a white solid. MS: 335.3 (M+H)⁺. HPLC (METHOD B1): R_T = 21.47 minutes.

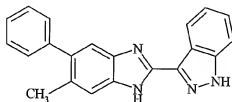
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(o) 3-(5-(Pyrid-3-yl)-1H-benzimidazol-2-yl)-1H-indazole



By proceeding in a manner similar to Example 235(i) above but using 4-(pyridine-3-yl) benzene-1,2-diamine [Reference Example 30(g)] there was prepared 3-(5-(pyrid-3-yl)-1H-benzoimidazol-2-yl)-1H-indazole as a white solid. MS: 312.2 (M+H)⁺. HPLC (METHOD B1): R_T = 8.58 minutes.

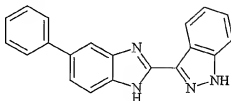
5 (p) 3-(6-Methyl-5-phenyl-1H-benzoimidazol-2-yl)-1H-indazole



By proceeding in a manner similar to Example 235(i) above but using 6-methylbiphenyl-3,4-diamine [Reference Example 30(h)] there was prepared 3-(6-methyl-5-phenyl-1H-benzoimidazol-2-yl)-1H-indazole as a white solid. MS: 325.3 (M+H)⁺. HPLC (METHOD B1): R_T = 14.48 minutes.

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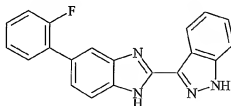
(q) 3-(5-Phenyl-1H-benzoimidazol-2-yl)-1H-indazole



By proceeding in a manner similar to Example 235(i) above but using 4-biphenyl-3,4-diamine [Reference Example 30(i)] there was prepared 3-(5-phenyl-1H-benzoimidazol-2-yl)-1H-indazole as a

15 white solid. MS: 311.2 (M+H)⁺. HPLC (Method D): R_T = 24.54 minutes.

(r) 3-(5-(2-Fluoro)phenyl)-1H-benzoimidazol-2-yl)-1H-indazole

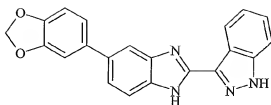


By proceeding in a manner similar to Example 235(i) above but using 2'-fluorobiphenyl-3,4-diamine [Reference Example 30(j)] there was prepared 3-(5-(2-fluoro)phenyl-1H-benzoimidazol-2-yl)-1H-indazole as a white solid. MS: 329.2 (M+H)⁺. HPLC (METHOD B1): R_T = 22.54 minutes.

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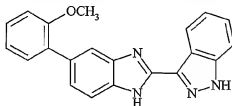
(s) 3-(5-(3,4-methylenedioxy)phenyl)-1H-benzoimidazol-2-yl)-1H-indazole

-392-



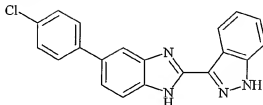
- By proceeding in a manner similar to Example 235(i) above but using 4-benzo[1,3]dioxol-5-ylbenzene-1,2-diamine [Reference Example 30(k)] there was prepared 3-(5-(5,6-methylenedioxy)phenyl)-1H-benzoimidazol-2-yl)-1H-indazole as a white solid. MS: 355.2 (M+H)⁺. HPLC (METHOD B1): R_T = 22.04 minutes.

(t) 3-(5-(2-Methoxy)phenyl)-1H-benzoimidazol-2-yl)-1H-indazole



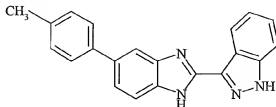
- By proceeding in a manner similar to Example 235(i) above but using 2'-methoxybiphenyl-3,4-diamine [Reference Example 30(l)] there was prepared 3-(5-(2-methoxy)phenyl)-1H-benzoimidazol-2-yl)-1H-indazole as a white solid. MS: 341.2 (M+H)⁺. HPLC (METHOD B1): R_T = 22.09 minutes.

(u) 3-(5-(4-Chloro)phenyl)-1H-benzoimidazol-2-yl)-1H-indazole



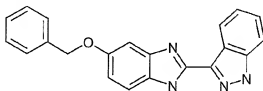
- By proceeding in a manner similar to Example 235(i) above but using 4'-chlorobiphenyl-3,4-diamine [Reference Example 30(m)] there was prepared 3-(5-(4-chloro)phenyl)-1H-benzoimidazol-2-yl)-1H-indazole as a white solid. MS: 345.2 (M+H)⁺. HPLC (METHOD B1): R_T = 23.71 minutes.

(v) 3-(5-(4-Methyl)phenyl)-1H-benzoimidazol-2-yl)-1H-indazole



By proceeding in a manner similar to Example 235(i) above but using 4'-methylbiphenyl-3,4-diamine [Reference Example 30(n)] there was prepared 3-(5-(4-methylphenyl)-1H-benzoimidazol-2-yl)-1H-indazole as a white solid. MS: 325.1 (M+H)⁺. HPLC (METHOD C1): R_T = 15.22 minutes.

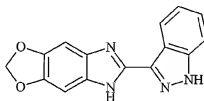
5 (w) 3-(5-Benzyloxy-1H-benzoimidazol-2-yl)-1H-indazole



By proceeding in a manner similar to Example 235(i) above but using 4-benzyloxybenzene-1,2-diamine [Reference Example 30(o)] there was prepared 3-(5-benzyloxy-1H-benzoimidazol-2-yl)-1H-indazole as a white solid. MS: 339.3 (M+H)⁺. HPLC (METHOD B1): R_T = 22.32 minutes.

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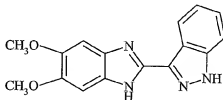
(x) 3-(5,6-Methylenedioxy-1H-benzoimidazol-2-yl)-1H-indazole



By proceeding in a manner similar to Example 235(i) above but using benzo[1,3]dioxole-5,6-diamine [Reference Example 30(p)] there was prepared 3-(5,6-methylenedioxy-1H-benzoimidazol-2-yl)-1H-

15 indazole as a white solid. LC-MS (METHOD B): R_T = 2.25 minutes; 279.22 (M+H)⁺.

(y) 3-(5,6-Dimethoxy-1H-benzoimidazol-2-yl)-1H-indazole

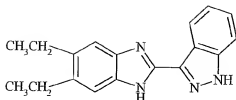


By proceeding in a manner similar to Example 235(i) above but using 4,5-dimethoxybenzene-1,2-

20 diamine [Reference Example 30(q)] there was prepared 3-(5,6-dimethoxy-1H-benzoimidazol-2-yl)-1H-
indazole as a white solid. LC-MS (METHOD B): R_T = 2.16 minutes; 295.26 (M+H)⁺.

(z) 3-(5,6-Diethyl-1H-benzoimidazol-2-yl)-1H-indazole

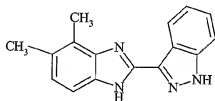
-394-



By proceeding in a manner similar to Example 235(i) above but using 4,5-diethylbenzene-1,2-diamine [Reference Example 30(r)] there was prepared 3-(5,6-diethyl-1H-benzimidazol-2-yl)-1H-indazole as a white solid. LC-MS (METHOD B): $R_T = 2.49$ minutes; 291.32 (M+H)⁺.

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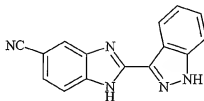
(aa) 3-(4,5-Dimethyl-1H-benzimidazol-2-yl)-1H-indazole



By proceeding in a manner similar to Example 235(i) above but using 3,4-dimethylbenzene-1,2-diamine there was prepared 3-(4,5-dimethyl-1H-benzimidazol-2-yl)-1H-indazole as a white solid.

10 LC-MS (METHOD B): $R_T = 2.31$ minutes; 263.24 (M+H)⁺.

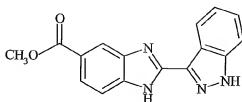
(ab) 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carbonitrile



15 By proceeding in a manner similar to Example 235(i) above but using 3,4-diaminobenzonitrile amine there was prepared 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carbonitrile as a white solid.

LC-MS (Method D): $R_T = 21.81$ minutes, MS: 260.10 (M+H)⁺.

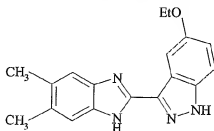
(ac) 3-(5-methoxycarbonyl-1H-benzimidazol-2-yl)-1H-indazole



By proceeding in a manner similar to Example 235(i) above but using 3,4-diaminobenzoic acid, methyl ester there was prepared 3-(5-methoxycarbonyl-1H-benzimidazol-2-yl)-1H-indazole as a white solid.

LC-MS (Method D): $R_T = 22.13$ minutes, 293.16 (M+H)⁺.

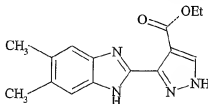
5 (ad) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-5-ethoxy-1H-indazole



By proceeding in a manner similar to Example 235(a) above but using 5-ethoxy-3-formyl-indazole-1-carboxylic acid *tert*-butyl ester [Reference Example 20(d)] there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-ethoxy-1H-indazole as a pale orange solid. MS: 307 (M+H)⁺. HPLC

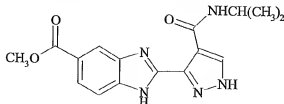
10 (METHOD B1): $R_T = 13.58$ minutes.

(ae) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-pyrazole-4-carboxylic acid ethyl ester



By proceeding in a manner similar to Example 235(a) above but using 3-formyl-pyrazole-4-carboxylic acid ethyl ester [Reference Example 6(i)] there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-pyrazole-4-carboxylic acid ethyl ester as a pale brown solid. LC-MS (METHOD B): 2.56 minutes; 285 (M+H)⁺.

(af) 2-(4-Isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid methyl ester

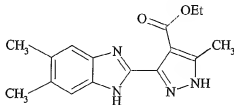


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By proceeding in a manner similar to Example 235(a) above but using 3-formyl-pyrazole-4-carboxylic acid isopropylamide [Reference Example 6(j)] and methyl-3,4-diamino benzoate there was prepared 2-

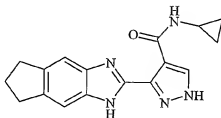
(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid methyl ester as a yellow solid. LC-MS (METHOD B): 2.99 minutes; 328 (M+H)⁺.

(ag) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-5-methyl-pyrazole-4-carboxylic acid ethyl ester



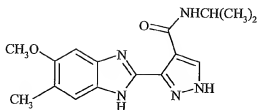
By proceeding in a manner similar to Example 235(a) above but using 3-formyl-5-methyl-pyrazole-4-carboxylic acid ethyl ester [Reference Example 6(k)] there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-pyrazole-4-carboxylic acid ethyl ester as a white solid. LC-MS (METHOD B): R_T = 2.59 minutes; 299 (M+H)⁺.

(ah) 3-(1,5,6,7-Tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide



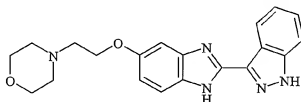
By proceeding in a manner similar to Example 235(a) above but using indane-5,6-diamine (130mg) and 3-formyl-1H-pyrazole-4-carboxylic acid cyclopropylamide [150 mg, Reference Example 6(q)] and subjecting the reaction product to chromatography on silica [eluting with ethyl acetate/ gradient 75 to 0%heptane] followed by trituration with acetone, there was prepared 3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide (31mg) as a white solid. LC-MS (Method A): R_T = 2.85 minutes, 308 (M+H)⁺.

(ai) 3-(5-Methoxy-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide



By proceeding in a manner similar to Example 235(a) above but using 3-formyl-pyrazole-4-carboxylic acid isopropylamide [198mg, Reference Example 6(j)] and 4-methoxy-5-methyl-benzene-1,2-diamine [166mg, Reference Example 29(b)] and subjecting the reaction product to flash chromatography on silica eluting with dichloromethane/methanol (95:5) followed by recrystallisation from a mixture of ethyl acetate and n-pentane there was prepared 3-(5-methoxy-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide (145mg) as a white solid. LC-MS (Method H): $R_T = 2.09$ minutes, $314.27 (M+H)^+$, $312.29 (M-H)^-$.

(aj) 3-[5-(2-Morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1H-indazole

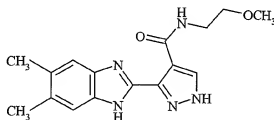


10

By proceeding in a manner similar to Example 235(i) above but using 4-(2-morpholin-4-yl-ethoxy)-benzene-1,2-diamine [Reference Example 29(c)] and subjecting the reaction product to preparative LC-MS there was prepared 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1H-indazole (25mg) as a white solid. MS: $364 (M+H)^+$. HPLC (METHOD B1): $R_T = 19.38$ minutes.

15

(ak) 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide



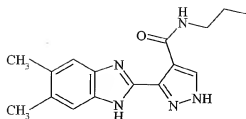
20

By proceeding in a manner similar to Example 235(i) above but using 4,5-dimethylbenzene-1,2-diamine and 3-formyl-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide [Reference Example 6(n)] there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide (87mg) as a cream solid. LC-MS (METHOD L): $R_T = 4.23$ minutes, $314.2 (M+H)^+$.

25

(al) 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid propylamide

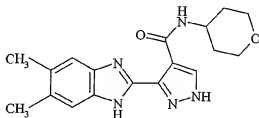
-398-



By proceeding in a manner similar to Example 6(i) above but using 4,5-dimethylbenzene-1,2-diamine and 3-formyl-1H-pyrazole-4-carboxylic acid propylamide [Reference Example 6(o)] there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid propylamide (73mg)

5 as a pale yellow solid. LC-MS (METHOD L): $R_T = 4.94$ minutes, 298.29 (M+H)⁺.

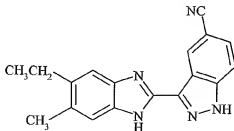
(am) 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide



10 By proceeding in a manner similar to Example 235(i) above but using 4,5-dimethyl-1,2-phenylenediamine and 3-formyl-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide [Reference Example 6(p)] and recrystallising the reaction product from methanol there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide (228mg) as a white solid. LC-MS (METHOD R): $R_T = 9.40$ minutes, 360 (M+H)⁺.

15

(an) 3-(5-Ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole-5-carbonitrile

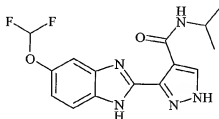


By proceeding in a manner similar to Example 235(i) above but using 4-ethyl-5-methyl-phenylene

20 diamine [Reference Example 30(a)] and 3-formyl-1H-indazole-5-carbonitrile [Reference Example 68]

there was prepared 3-(5-ethyl-6-methyl-1H-benzoimidazol-2-yl)-1H-indazole-5-carbonitrile (133mg) as a pale yellow solid. MS: 302 (M+H)⁺. HPLC (METHOD B1): R_T = 16.45 minutes.

(ao) 3-(5-Difluoromethoxy-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide

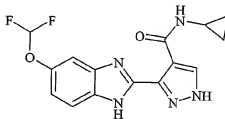


5

By proceeding in a manner similar to Example 235(i) above but using 4-difluoromethoxy-benzene-1,2-diamine [Reference Example 30(y)] and 3-formyl-pyrazole-4-carboxylic acid isopropylamide [Reference Example 6(j)] there was prepared 3-(5-difluoromethoxy-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide (118mg) as a white solid. LC-MS (METHOD L): R_T =

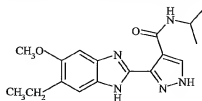
10 10.46 minutes, 336.19 (M+H)⁺.

(ap) 3-(5-Difluoromethoxy-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide



15 By proceeding in a manner similar to Example 235(ao) above but using 3-formyl-1H-pyrazole-4-carboxylic acid cyclopropylamide [Reference Example 6(q)] there was prepared 3-(5-difluoromethoxy-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide (63mg) as a white solid. LC-MS (METHOD L): R_T = 10.18 minutes, 334.17 (M+H)⁺.

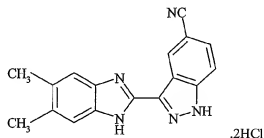
20 (aq) 3-(6-Ethyl-5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide



By proceeding in a manner similar to Example 235(i) but using 4-ethyl-5-methoxy-benzene-1,2-diamine [200 mg, Reference Example 30(z)] and 3-formyl-pyrazole-4-carboxylic acid isopropylamide

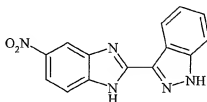
[Reference Example 6(j)] there was prepared 3-(6-ethyl-5-methoxy-1H-benzotriazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide (115 mg) as an off-white solid. LC-MS (METHOD L): R_T = 11.34 minutes, 328.24 (M+H)⁺.

- 5 (ar) 3-(5,6-Dimethyl-1H-benzotriazol-2-yl)-1H-indazole-5-carbonitrile dihydrochloride



- By proceeding in a manner similar to Example 235(i) above but (i) using 4,5-dimethyl-phenylene diamine and 3-formyl-1H-indazole-5-carbonitrile [Reference Example 68] (ii) treating a suspension of
 10 the reaction product in methanol with a solution of hydrochloric acid (4M) in 1,4-dioxane followed by evaporation of the mixture (iii) trituration of the residue with methanol and (iv) recrystallisation from diethyl ether, there was prepared 3-(5,6-dimethyl-1H-benzotriazol-2-yl)-1H-indazole-5-carbonitrile dihydrochloride (133mg) as an off-white solid. LC-MS (METHOD B): R_T = 2.32 minutes. MS: 288 (M+H)⁺.

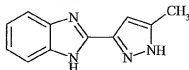
- 15 (as) 3-(5-nitro-1H-benzotriazol-2-yl)-1H-indazole



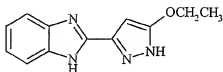
- By proceeding in a manner similar to Example 235(a) above but using 4-nitrophenylenediamine there was prepared 3-(5-nitro-1H-benzotriazol-2-yl)-1H-indazole as red solid. MS: 280.17 (M+H)⁺.
 20 HPLC (Method B1): R_T = 3.00 minutes.

EXAMPLE 236

2-(5-Methyl-1H-pyrazol-3-yl)-1H-benzotriazole

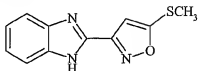


A mixture of o-phenylenediamine (1.08g) and 5-methylpyrazole-3-carboxylic acid (1.266g) was finely ground and the finely ground material was heated at 160°C for 3 hours and then cooled to ambient temperature. The reaction mixture was recrystallised from ethyl alcohol (50mL) to give a light blue solid (0.27g). The filtrate gave another crop (0.1g) on standing. The combined solids were
 5 recrystallised from ethyl alcohol to give 2-(5-methyl-1H-pyrazol-3-yl)-1H-benzimidazole (223mg) as a lilac coloured solid, mp 322-324°C. [Elemental analysis:- C, 66.54%; H, 4.80%; N, 28.14%. Calculated for $C_{11}H_{10}N_4$:- C, 66.64%; H, 5.09%; N, 28.27%].

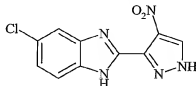
EXAMPLE 237**10** 2-(5-Ethoxy-1H-pyrazol-3-yl)-1H-benzimidazole

A mixture of trifluoroacetic acid (6mL) and 2-(5-ethoxy-1H-pyrazol-3-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole (300mg, Reference Example 11) was stirred at 50°C for 1.5 hours. The reaction mixture was evaporated and the residue was partitioned between ethyl acetate and water
 15 (pH 10). The organic layer was dried and then evaporated. The residue was subjected to chromatography on silica eluting with a mixture of dichloromethane and methanol (9:1, v/v) and then recrystallised from toluene to give 2-(5-ethoxy-1H-pyrazol-3-yl)-1H-benzimidazole (0.1g) as a colourless solid, mp 217-219.5°C. [Elemental analysis:- C, 62.26%; H, 5.23%; N, 23.44%. Calculated for $C_{12}H_{12}N_4O$:- C, 63.15%; H, 5.30%; N, 24.55%].

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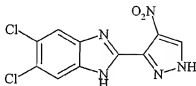
EXAMPLE 2382-(5-Methylsulfanyl-isoxazol-3-yl)-1H-benzimidazole

A mixture of 2-(5-methylsulfanyl-isoxazol-3-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole (160mg, Reference Example 12), methanol (12mL) and concentrated aqueous
 25 hydrochloric acid (2.45mL) were heated at reflux for four hours, then cooled and then evaporated. The residue was treated with aqueous sodium bicarbonate and the mixture was extracted with ethyl acetate. The extracts were dried and then evaporated to give 2-(5-methylsulfanyl-isoxazol-3-yl)-1H-benzimidazole (96mg) as an off white solid, mp 179-181°C. 1H -NMR $[(CD_3)_2SO]$: δ 4.65 (s, 3H),
 30 9.00 (s, 1H), 9.15-9.6 (m, 4H).

EXAMPLE 239(a) 5-Chloro-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole

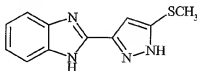
- 5 A solution of 4-chloro-benzene-1,2-diamine (500mg) in hydrochloric acid (4N) was treated with 4-nitro-pyrazole-3-carboxylic acid (826mg) then heated at reflux temperature, under nitrogen. The reaction mixture was cooled to room temperature when the pH was adjusted to 8 by addition of ammonium hydroxide and the mixture was extracted with ethyl acetate. The extracts were evaporated to give 5-chloro-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole.

10

(b) 5,6-dichloro-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole

By proceeding in a similar manner to Example 239(a) above but using 4,5-dichloro-1,2-diaminobenzene there was prepared 5,6-dichloro-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole.

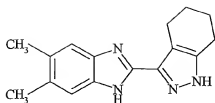
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EXAMPLE 240(Benzoimidazol-2-yl)-5-methylthio-3-pyrazole

- A mixture of 1-[(3,3-bis(methylthio))benzoimidazol-2-yl]propen-2-one [5.5g, Reference Example 15],
 20 hydrazine hydrate (1.02g) and acetonitrile (50mL) was stirred at reflux for 18 hours. The reaction mixture was cooled, and the precipitate was isolated by filtration. Recrystallisation from aqueous ethanol provided (benzoimidazol-2-yl)-5-methylthio-3-pyrazole (3.36g) as a beige crystalline solid, m.p. 242°C. [Elemental analysis: Found: C 57.8; H 4.5; N 24.0. Calculated for C₁₁H₁₀N₄S: C 57.37; H 4.38; N 24.33].

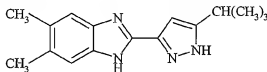
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EXAMPLE 241(a) 3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-4,5,6,7-tetrahydro-1H-indazole



- 4,5-Dimethylbenzene-1,2-diamine (90mg) and 4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid [110mg, Reference Example 17(a)] were mixed in a glass vial then subjected to microwave radiation (900W, domestic oven) twice for two minutes. The resulting solid was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and hexane (85:15, v/v) to give 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-indazole (30mg) as a pale brown solid. LC-MS (METHOD B): $R_T = 2.28$ minutes; 267 (M+H)⁺.

(b) 2-(5-Isopropyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole

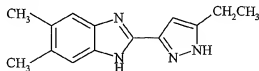


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By proceeding in a manner similar to Example 241 (a) above, but using 5-isopropyl-1H-pyrazole-3-carboxylic acid [Reference Example 17(b)] there was prepared 2-(5-isopropyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole (80mg) as a brown solid. LC-MS (METHOD B): $R_T = 2.27$ minutes; 255 (M+H)⁺.

15

(c) 2-(5-Ethyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole

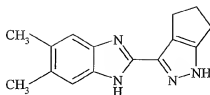


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By proceeding in a manner similar to Example 241(a) above but using 5-ethyl-1H-pyrazole-3-carboxylic acid [Reference Example 17(c)], and triturating the brown solid reaction product with a mixture of ethyl acetate and hexane (1:1, v/v), there was prepared 2-(5-ethyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole as a light brown solid. LC-MS (METHOD B): $R_T = 2.22$ minutes; 241 (M+H)⁺.

(d) 5,6-Dimethyl-2-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-1H-benzimidazole

-404-

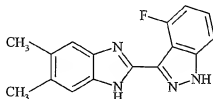


By proceeding in a manner similar to Example 214(a) above but using 1,4,5,6-tetrahydro-cyclopentapyrazole-3-carboxylic acid [Reference Example 17(f)] and triturating the reaction product with ethyl acetate, ether and methanol, there was prepared 5,6-dimethyl-2-(1,4,5,6-tetrahydro-

- 5 cyclopentapyrazole-3-yl)-1H-benzimidazole (50mg) as an off-white solid. MS: 253 (M+H)⁺. HPLC (METHOD B1): R_T = 11.17 minutes.

EXAMPLE 242

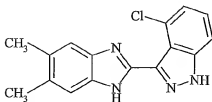
- (a) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-4-fluoro-1H-indazole



10

A mixture of 4,5-dimethylbenzene-1,2-diamine (70mg) and 4-fluoro-1H-indazole-3-carbaldehyde [80mg, Reference Example 20(b)] in dimethylformamide (8ml) was heated to 120°C for 30 minutes and then at 100°C for 16 hours. The reaction mixture was cooled, then diluted with ethyl acetate and then washed five times with brine. The organic phase was dried over magnesium sulfate and then
 15 evaporated. The residue was subjected to flash column chromatography on silica eluting with a mixture of 40/60 petrol and ethyl acetate (1:5, v/v) to give 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4-fluoro-1H-indazole (104mg) as a light brown solid. MS: 281 (M+H)⁺. HPLC (METHOD B1): R_T = 10.08 minutes.

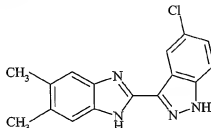
- 20 (b) 4-Chloro-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole



By proceeding in a manner similar to Example 242(a) above but using 4-chloro-3-formyl-indazole-1-carboxylic acid *tert*-butyl ester [Reference Example 20(e)] there was prepared 4-chloro-3-(5,6-

dimethyl-1H-benzoimidazol-2-yl)-1H-indazole (25mg) as an off-white solid. MS: 299 (M+H)⁺.
HPLC (METHOD B1): R_T = 10.59 minutes.

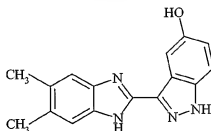
(c) 3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-5-chloro-1H-indazole



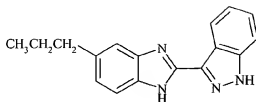
By proceeding in a manner similar to Example 242(a) above but using 5-chloro-1H-indazole-3-carbaldehyde [Reference Example 6(h)] there was prepared 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-5-chloro-1H-indazole (25mg) as a pale brown solid. LC-MS (METHOD D): R_T = 24.24 minutes, 299 (M+H)⁺.

EXAMPLE 243

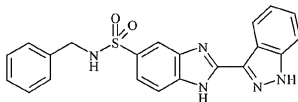
3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1H-indazol-5-ol



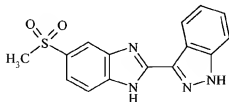
A solution of 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-5-methoxy-1H-indazole [34mg, Example 235(b)] at 0°C was treated with a solution of boron tribromide in dichloromethane (0.30mL, 1M). The mixture was then heated at reflux temperature for 4 hours, then cooled and then treated dropwise with water. The pH was adjusted to between 7 and 8 by the addition of saturated aqueous sodium bicarbonate solution and this mixture was then extracted twice with ethyl acetate. The combined extracts were washed with brine, then dried over magnesium sulfate and then evaporated. The yellow solid residue was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and triethylamine (99:1, v/v) to yield 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-indazol-5-ol (23mg) as a white solid. LC-MS (METHOD B): R_T = 2.19 minutes; 279 (M+H)⁺.

EXAMPLE 244(a) 3-(5-n-Propyl-1H-benzoimidazol-2-yl)-1H-indazole

- A stirred solution of 4-propyl-benzene-1,2-diamine [57mg, Reference Example 30(d)] and sodium bisulfite (40 mg) in dimethylformamide (2 ml) was treated with indazole-3-carboxaldehyde [Reference Example 6(l)]. The reaction mixture was heated in a Smith Creator microwave at 200°C for 13 minutes then partitioned between ethyl acetate and water. The organic layer was washed with brine, then dried over magnesium sulfate and then evaporated. The residue was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and hexane (3:1) to give 3-(5-n-propyl-1H-benzoimidazol-2-yl)-1H-indazole (74 mg) as a pale brown solid. MS: 277.3 (M+H)⁺. HPLC (METHOD B1): R_T = 12.81 minutes.

(b) 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-sulfonic acid benzylamide

- By proceeding in a manner similar to Example 244(a) above but using 3,4-diamino-N-benzylbenzenesulfonamide [Reference Example 30(x)] and heating at 230°C there was prepared 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-sulfonic acid benzylamide (235mg) as a white solid. LC-MS (METHOD L): R_T = 6.35 minutes, 404.20 (M+H)⁺.

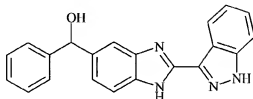
(c) 3-(5-Methanesulfonyl-1H-benzoimidazol-2-yl)-1H-indazole

By proceeding in a manner similar to Example 244(a) above but using 4-methanesulfonyl-benzene-1,2-diamine [Reference Example 49(f)] and heating at 210°C there was prepared 3-(5-methanesulfonyl-1H-

benzimidazol-2-yl)-1H-indazole (105mg) as a white solid. LC-MS (METHOD 1): $R_T = 5.71$ minutes, $313.23 (M+H)^+$.

EXAMPLE 245

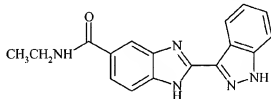
5 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-phenyl-methanol



- A stirred solution of [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-phenyl-methanol [200mg, Example 234(c)] in tetrahydrofuran (10mL), at -78°C and under an atmosphere of nitrogen, was treated dropwise with a solution of diisobutylaluminium hydride in tetrahydrofuran (1.18mL, 1N). The reaction mixture was warmed to ambient temperature, then stirred for 16 hours and then partitioned between ether and sodium hydroxide solution (2N). The organic phase was washed with water, then with brine, then dried over magnesium sulfate and then evaporated. The residue was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and hexane (3:1, v/v) to give [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-phenyl-methanol (161mg) as a white solid. LC-MS (Method D): $R_T = 21.89$ minutes, $341.3 (M+H)^+$.

EXAMPLE 246

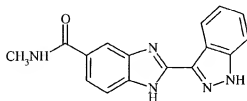
(a) [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, ethylamide



- A stirred solution of [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid [130mg, Example 247(a)], hydroxybenzotriazole (189mg) and diisopropyl ethylamine (732μL) in dimethylformamide (3mL) was treated with ethylamine and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (267mg). The reaction mixture was heated at 80°C overnight and then partitioned between ethyl acetate and 5% citric acid. The aqueous layer was re-extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate solution, then with brine, then dried over magnesium sulfate and then evaporated. The residual oil was subjected to

preparative HPLC to give [2-(indazol-3-yl)-1H-benzoimidazol-5-yl]-carboxylic acid, ethylamide as a white solid. LC-MS (METHOD B): $R_T = 2.37$ minutes; $306.27 (M+H)^+$.

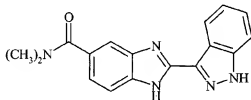
(b) [2-(Indazol-3-yl)-1H-benzoimidazol-5-yl]-carboxylic acid, methylamide



5

By proceeding in a manner similar to Example 246(a) above but using methylamine, there was prepared [2-(indazol-3-yl)-1H-benzoimidazol-5-yl]-carboxylic acid, methylamide as a white solid. LC-MS (METHOD B): $R_T = 2.28$ minutes; $292.30 (M+H)^+$.

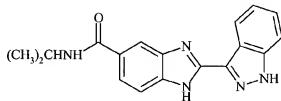
10 (c) [2-(Indazol-3-yl)-1H-benzoimidazol-5-yl]-carboxylic acid, dimethylamide



By proceeding in a manner similar to Example 246(a) above but using dimethylamine, there was prepared [2-(indazol-3-yl)-1H-benzoimidazol-5-yl]-carboxylic acid, dimethylamide as a white solid. LC-MS (METHOD B): $R_T = 2.38$ minutes; $306.27 (M+H)^+$.

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(d) [2-(Indazol-3-yl)-1H-benzoimidazol-5-yl]-carboxylic acid, isopropylamide

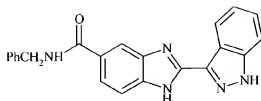


By proceeding in a manner similar to Example 246(a) above but using isopropylamine, there was prepared [2-(indazol-3-yl)-1H-benzoimidazol-5-yl]-carboxylic acid, isopropylamide as a white solid.

20 LC-MS (METHOD B): $R_T = 2.48$ minutes; $320.30 (M+H)^+$.

(e) [2-(Indazol-3-yl)-1H-benzoimidazol-5-yl]-carboxylic acid, benzylamide

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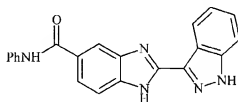


By proceeding in a manner similar to Example 246(a) above but using benzylamine, there was prepared [2-(indazol-3-yl)-1H-benzoimidazol-5-yl]-carboxylic acid, benzylamide as a white solid.

LC-MS (METHOD B): $R_T = 2.68$ minutes; 368.27 (M+H)⁺.

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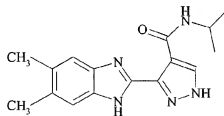
(f) [2-(indazol-3-yl)-1H-benzoimidazol-5-yl]-carboxylic acid, benzamide



By proceeding in a manner similar to Example 246 (a) above but using aniline, there was prepared [2-(indazol-3-yl)-1H-benzoimidazol-5-yl]-carboxylic acid, benzamide as a white solid.

10 LC-MS (METHOD B): $R_T = 2.73$ minutes; 354.26 (M+H)⁺.

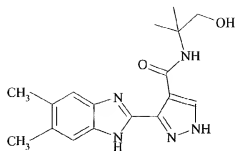
(g) 3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide



By proceeding in a manner similar to Example 246(a) above but using 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-pyrazole-4-carboxylic acid [Example 247(b)] and isopropylamine, and subjecting the reaction product to flash chromatography on silica eluting with a mixture of dichloromethane and methanol (19:1, v/v), there was prepared 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide as an off-white solid. LC-MS (METHOD B): $R_T = 2.67$ minutes; 298 (M+H)⁺.

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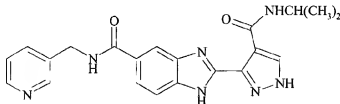
(h) 3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide



- By proceeding in a manner similar to Example 246(a) above but using 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-pyrazole-4-carboxylic acid [Example 247(b)] and 2-amino-2-methyl-1-propanol, and subjecting the reaction product to flash chromatography on silica eluting with a mixture of dichloromethane and methanol (19:1, v/v), there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide as a pale yellow solid.

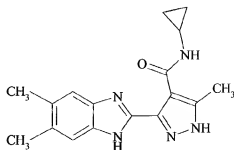
LC-MS (METHOD B): $R_T = 2.63$ minutes; 328 (M+H)⁺.

- (i) 2-(4-Isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide



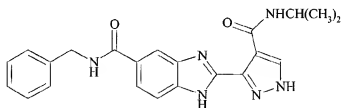
- By proceeding in a manner similar to Example 246(a) above but using 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid [Example 247(c)] and 3-(aminomethyl)pyridine there was prepared 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide as a white solid. LC-MS (METHOD B): $R_T = 2.49$ minutes; 404 (M+H)⁺.

- (j) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid cyclopropylamide



- By proceeding in a manner similar to Example 246(a) above but using 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-pyrazole-4-carboxylic acid [Example 247(d)] and cyclopropylamine, and subjecting the reaction product to flash chromatography on silica eluting with a mixture of dichloromethane and methanol (19:1, v/v), there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid cyclopropylamide as a white solid. LC-MS (METHOD B): $R_T = 2.67$ minutes; 310 (M+H)⁺.

- (k) 2-(4-Isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid phenylmethyl-amide

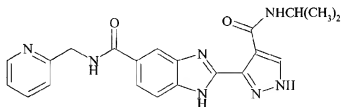


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- By proceeding in a manner similar to Example 246(a) above but using 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid [Example 247(c)] and benzylamine there was prepared 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid phenylmethyl-amide as a pale yellow solid. LC-MS (METHOD B): $R_T = 3.17$ minutes; 403 (M+H)⁺.

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- (l) 2-(4-Isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide



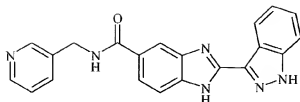
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- By proceeding in a manner similar to Example 246(a) above but using 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid [Example 247(c)] and 2-(aminomethyl)pyridine there was prepared 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide as an off-white solid. LC-MS (Method D): $R_T = 9.33$ minutes, 367.28 (M+H)⁺.

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- (m) 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide

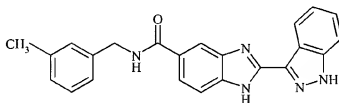
-412-



By proceeding in a manner similar to Example 246(a) above but using 3-(aminomethyl)pyridine there was prepared 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide (42.2mg) as an off white solid. LC-MS (Method L): $R_T = 4.96$ minutes, 367.19 (M-H)⁺.

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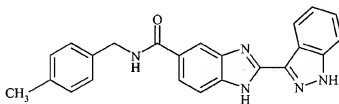
(n) 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 3-methyl-benzylamide



By proceeding in a manner similar to Example 246(a) above but using 3-methylbenzylamine there was prepared 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 3-methyl-benzylamide (33.4mg) as

10 a white solid. MS: 382.52 (M+H)⁺. HPLC (Method B1): $R_T = 16.22$ minutes.

(o) 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-methyl-benzylamide

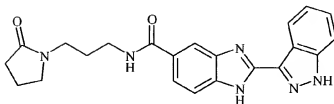


By proceeding in a manner similar to Example 246(a) above but using 4-methylbenzylamine there was prepared 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-methyl-benzylamide (63.5mg) as

15

a white solid. MS: 382.54 (M+H)⁺. HPLC (Method B1): $R_T = 16.14$ minutes.

(p) 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide

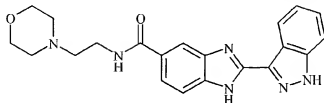


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By proceeding in a manner similar to Example 246(a) above but using 1-(3-aminopropyl)-2-pyrrolidinone there was prepared 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide (68.1mg) as a white solid. MS: 401.13 (M-H)⁻. HPLC (Method B1): R_T = 11.29 minutes.

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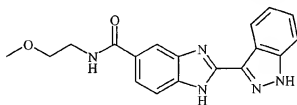
(q) 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide



By proceeding in a manner similar to Example 246(a) above but using 4-(2-aminoethyl)morpholine there was prepared 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-

10 ethyl)-amide (70.8mg) as a white solid. MS: 389.12 (M-H)⁻. HPLC (Method B1): R_T = 8.51 minutes.

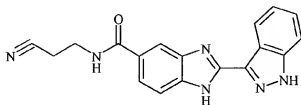
(r) 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide



By proceeding in a manner similar to Example 246(a) above but using 2-methoxyethylamine there was prepared 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide (55.2mg) as a white solid. MS: 336.52 (M+H)⁺. HPLC (Method B1): R_T = 11.30 minutes.

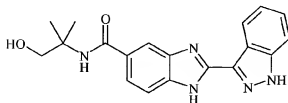
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(s) 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2-cyano-ethyl)-amide



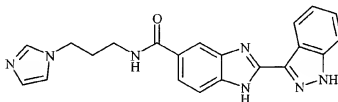
20 By proceeding in a manner similar to Example 246(a) above but heating the reaction at 50°C and using 3-aminopropionitrile there was prepared 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2-cyano-ethyl)-amide (15.4mg) as a white solid. MS: 331.15 (M+H)⁺, 329.17 (M-H)⁻. HPLC (Method B1): R_T = 12.72 minutes.

- (t) 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide



- 5 By proceeding in a manner similar to Example 246(a) above but heating the reaction at 50°C and using 2-amino-2-methyl-1-propanol there was prepared 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide (29.6mg) as a brown oil. LC-MS (Method L): $R_T = 10.57$ minutes, 350.16 (M+H)⁺, 348.18 (M-H)⁻.

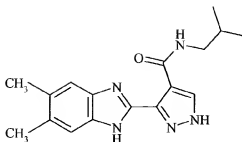
- 10 (u) 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (3-imidazol-1-yl-propyl)-amide



By proceeding in a manner similar to Example 246(a) above but using 1-(3-aminopropyl)imidazole there was prepared 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (3-imidazol-1-yl-propyl)-amide (31.9mg) as a white solid. LC-MS (Method B): $R_T = 8.45$ minutes, 386.22 (M+H)⁺, 384.26

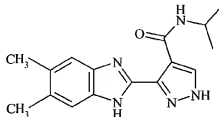
- 15 (M-H)⁻.

- (v) 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isobutyl-amide



By proceeding in a manner similar to Example 246(g) above but using isobutylamine there was prepared 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isobutyl-amide (101mg) as a white solid. LC-MS (METHOD M): $R_T = 9.38$ minutes, 312 (M+H)⁺.

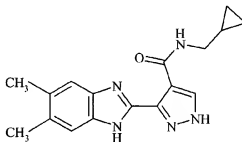
- 5 (w) 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide



By proceeding in a manner similar to Example 246(g) above but using isopropylamine there was prepared 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide (100mg) as a white solid. LC-MS (METHOD L): $R_T = 7.21$ minutes, 298 (M+H)⁺.

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- (x) 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylmethyl-amide

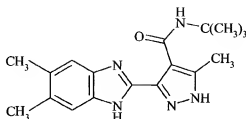


By proceeding in a manner similar to Example 246(g) above but using (aminomethyl)cyclopropane

- 15 there was prepared 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylmethyl-amide (105mg) as a white solid. LC-MS (METHOD M): $R_T = 8.77$ minutes, 310 (M+H)⁺.

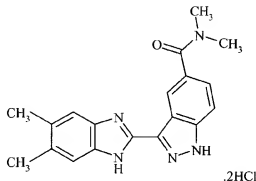
- (y) 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid tert-butylamide

20



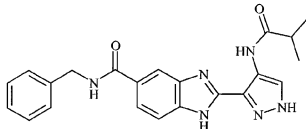
By proceeding in a manner similar to Example 246(j) above but using *tert*-butylamine there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid *tert*-butylamide (57mg) as an off-white solid. LC-MS (METHOD M): $R_T = 13.86$ minutes, $326 (M+H)^+$.

- 5 (z) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-indazole-5-carboxylic acid dimethylamide dihydrochloride



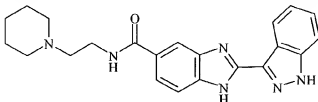
- By proceeding in a manner similar to Example 246(j) above, but (i) using 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole-5-carboxylic acid [97mg, Example 263] and dimethylamine hydrochloride (23mg), (ii) carrying out the reaction at ambient temperature overnight, and (iii) subjecting the reaction product to flash column chromatography [eluting with ethyl acetate to ethyl acetate/methanol (97:3, v/v)] followed by treatment with 4M hydrogen chloride in 1,4-dioxane and trituration with dichloromethane and diethyl ether there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole-5-carboxylic acid dimethylamide dihydrochloride (8mg) as a white solid. LC-MS (METHOD M): $R_T = 9.37$ minutes, $320 (M+H)^+$.
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- 15

- (aa) 2-(4-isobutrylamino-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide



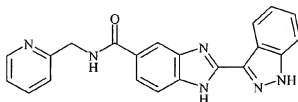
- 20 By proceeding in a manner similar to Example 246(a) above but using 2-(4-isobutrylamino-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid [Reference Example 35] and benzylamine there was prepared 2-(4-isobutrylamino-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide (17mg) as a white solid. LC-MS (METHOD L): $R_T = 11.00$ minutes, $403 (M+H)^+$.

- (ab) 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2-piperidin-1-yl-ethyl)-amide



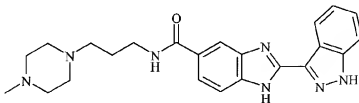
- By proceeding in a manner similar to Example 246(a) above but using 1-(2-aminoethyl)piperidine, and
 5 heating the reaction mixture at 50°C for 6 hours, there was prepared 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2-piperidin-1-yl-ethyl)-amide as an oil. MS: 387.22 (M+H)⁺. HPLC (Method I): R_T = 5.03 minutes.

- (ac) 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide



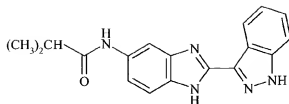
- 10 By proceeding in a manner similar to Example 246(ab) above but using (2-aminomethyl)pyridine there was prepared 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide as an off-white solid. MS: 367.28 (M+H)⁺. HPLC (Method B1): R_T = 9.33 minutes.

- 15 (ad) 2-(1H-Indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide



- By proceeding in a manner similar to Example 246(ab) above but using 4-(3-(aminopropyl))-1-methyl piperazine there was prepared 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide as an oil. MS: 416.21 (M+H)⁺. HPLC (Method I): R_T = 4.46 minutes.
 20

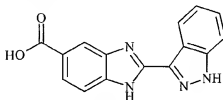
- (ae) N-[2-(1H-Indazol-3-yl)-1H-benzoimidazol-5-yl]-isobutyramide



- By proceeding in a manner similar to Example 246(ab) above but using isobutyric acid and 2-(1H-indazol-3-yl)-3H-benzimidazol-5-amine [Example 265] there was prepared N-[2-(1H-indazol-3-yl)-11H-benzimidazol-5-yl]-isobutyramide as an off-white solid. MS: 320.23 (M+H)⁺. HPLC (Method B1): R_T = 19.28 minutes.

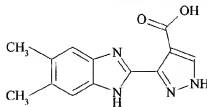
EXAMPLE 247

- (a) [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid

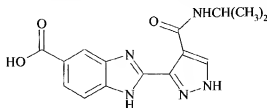


- 10 A stirred solution of 3-(5-methoxycarbonyl-1H-benzimidazol-2-yl)-1H-indazole [84.5mg, Example 235(ac)] and sodium hydroxide (74mg) in tetrahydrofuran (4mL) and water (2mL) was heated at 75°C overnight. The reaction mixture was evaporated and the oily residue was partitioned between ethyl acetate and water. The aqueous layer was acidified to pH 6 and extracted with ethyl acetate. The organic layers was dried over magnesium sulfate and then evaporated to give [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid (80mg) as an oil. MS: 279.14 (M+H)⁺. HPLC (METHOD H): R_T = 2.81 minutes.

- (b) 3-(5,6-Dimethyl-1H-benzimidazol-5-yl)-pyrazole-4-carboxylic acid

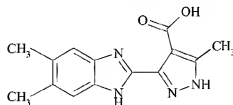


- 20 By proceeding in a manner similar to Example 247(a) above but using 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-pyrazole-4-carboxylic acid ethyl ester [Example 235(ae)] and carrying out the reaction at 60°C there was prepared 3-(5,6-dimethyl-1H-benzimidazol-5-yl)-pyrazole-4-carboxylic acid as a white solid. LC-MS (METHOD B): R_T = 2.17 minutes; 257 (M+H)⁺.

(c) 2-(4-Isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid

By proceeding in a manner similar to Example 247(a) above but using 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid methyl ester [Example 235(a)], replacing the

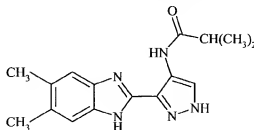
- 5 tetrahydrofuran with methanol and carrying out the reaction at 65°C, there was prepared 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid as a pale brown solid which was used without further purification. LC-MS (METHOD B): $R_T = 2.67$ minutes; 314 (M+H)⁺.

(d) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-5-methyl-pyrazole-4-carboxylic acid

10

By proceeding in a manner similar to Example 247(a) above but using 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-pyrazole-4-carboxylic acid ethyl ester [Example 235(ag)], replacing the tetrahydrofuran with methanol and carrying out the reaction at 65°C, there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-pyrazole-4-carboxylic acid as a white solid. LC-MS

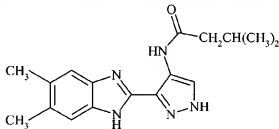
- 15 (METHOD B): $R_T = 2.75$ minutes; 271 (M+H)⁺.

EXAMPLE 248(a) N-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isobutyramide

- 20 A stirred solution of 5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [83mg, Example 233(c)] and diisopropylethylamine (256μL) in dichloromethane (4mL) was treated with isobutyryl chloride (115μL). The reaction mixture was stirred for 30 minutes at room temperature then treated with piperidine (500μL) and stirring was continued for a further hour. The reaction mixture was

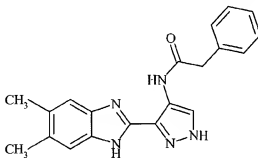
partitioned between 5% citric acid. The organic layer was dried over magnesium sulfate and then evaporated. The residue was subjected to flash chromatography on silica eluting with a mixture of hexane and ethyl acetate to give N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isobutyramide (49mg) as a white solid. MS: 298.28 (M+H)⁺. HPLC (METHOD B1): R_T = 14.66 minutes.

(b) N-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-butylamide



By proceeding in a manner similar to Example 248(a) above but using isovaleryl chloride there was prepared N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-butylamide as a white solid. MS: 312.28 (M+H)⁺. HPLC (METHOD B1): R_T = 15.28 minutes.

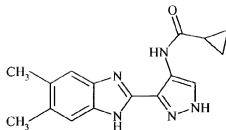
(c) N-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-phenyl-acetamide



By proceeding in a manner similar to Example 248(a) above but using phenylacetyl chloride there was prepared N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-phenyl-acetamide as a white solid. LC-MS (METHOD B): R_T = 2.83 minutes, 346.18 (M+H)⁺.

(d) Cyclopropanecarboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide

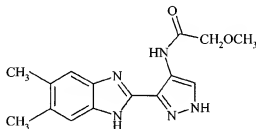
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By proceeding in a manner similar to Example 248(a) above but using cyclopropanecarbonyl chloride, there was prepared cyclopropanecarboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide as a white solid. MS: 296.28 (M+H)⁺. HPLC (METHOD B1): R_T = 13.50 minutes.

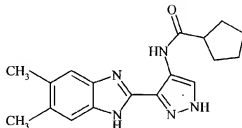
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(e) Methoxyacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



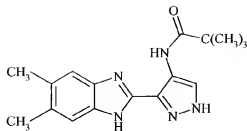
10 By proceeding in a manner similar to Example 248(a) above but using methoxyacetyl chloride, there was prepared methoxyacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide as a white solid. MS: 300.33 (M+H)⁺. HPLC (METHOD C1): R_T = 14.25 minutes.

(f) Cyclopentanecarboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



15 By proceeding in a manner similar to Example 248(a) above but using cyclopentylcarbonyl chloride, there was prepared cyclopentanecarboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide as a white solid. MS: 324.39 (M+H)⁺. HPLC (METHOD B1): R_T = 17.64 minutes.

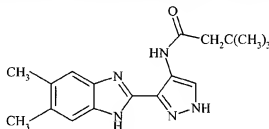
(g) Trimethylacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



By proceeding in a manner similar to Example 248(a) above but using trimethylacetyl chloride, there was prepared trimethylacetyl acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide as a white solid. MS: 312.39 (M+H)⁺. HPLC (METHOD B1): R_T = 19.52 minutes.

5

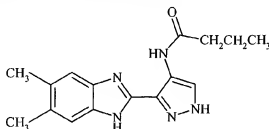
(h) tert-Butylacetyl acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



By proceeding in a manner similar to Example 248(a) above but using *tert*-butylacetyl chloride, there was prepared tert-butylacetyl acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide as a white solid. MS: 326.29 (M+H)⁺. HPLC (METHOD B1): R_T = 19.52 minutes.

10

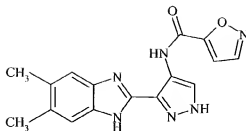
(i) Butanoic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



By proceeding in a manner similar to Example 248(a) above but using butyryl chloride, there was prepared butanoic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide as a white solid. MS: 298.34 (M+H)⁺. HPLC (METHOD B1): R_T = 15.07 minutes.

15

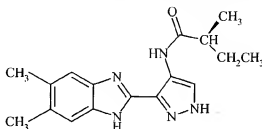
(j) Isoxazole-5-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



By proceeding in a manner similar to Example 248(a) above but using isoxazole-5-carbonyl chloride, there was prepared isoxazole-5-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide as a white solid. MS: 323.16 (M+H)⁺. HPLC (METHOD B1): R_T = 10.01 minutes.

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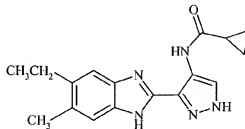
(k) S(+)-2-Methylbutanoic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



By proceeding in a manner similar to Example 248(a) above but using S(+)-2-methyl butyryl chloride, there was prepared S(+)-2-methylbutanoic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-

10 4-yl]-amide as a white solid. MS: 312.18 (M+H)⁺. HPLC (METHOD B1): R_T = 11.15 minutes.

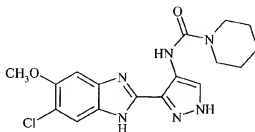
(l) Cyclopropanecarboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



15 By proceeding in a manner similar to Example 248(a) above but using 3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [Example 233(d)] and cyclopropanecarbonyl chloride, there was prepared cyclopropanecarboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide as a white solid. MS: 310.32 (M+H)⁺. HPLC (METHOD B1): R_T = 8.88 minutes.

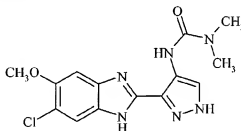
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- (m) Piperidine-1-carboxylic acid[3-(6-chloro-5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide

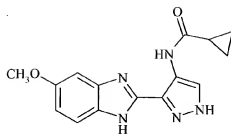


- By proceeding in a manner similar to Example 248(a) above but (i) treating a solution of 3-(6-chloro-5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine [0.2g, Example 233(e)] and diisopropylethylamine (392mg, 4 eq) in tetrahydrofuran (25mL) with piperidinecarbonyl chloride (450mg, 4 eq), stirring overnight at ambient temperature, and evaporating the reaction mixture, (ii) triturating the reaction product with water (30 mL) and ethyl acetate (50 mL) and extracting with aqueous layer with ethyl acetate, (iii) combining the organic phases, drying over magnesium sulfate, then evaporating (iv) chromatographing the residue on silica gel (ethyl acetate), (v) triturating the partially purified material with ethyl acetate (15mL) for 1.5 hours and filtering, and (vi) evaporating the filtrate and chromatographing the residue on silica gel (ethyl acetate/heptane gradient of 20-0%) there was prepared piperidine-1-carboxylic acid[3-(6-chloro-5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (50 mg) as a yellow solid, mp >310°C. LC-MS (Method E) R_T = 3.25 minutes, 374 (M+H)⁺.

- (n) 3-[3-(6-Chloro-5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethylurea

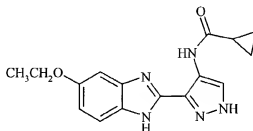


- By proceeding in a similar manner to Example 248(m) above but using N,N-dimethylcarbonyl chloride there was prepared 3-[3-(6-chloro-5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethylurea as a yellow solid, mp >300°C. LC-MS (Method E): R_T = 2.4 minutes, 335 (M+H)⁺.
- (o) Cyclopropanecarboxylic acid [3-(5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide



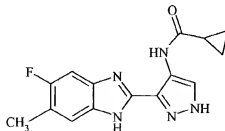
- By proceeding in a manner similar to Example 248(a) above but using 3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [282mg, Example 233(f)] and cyclopropanecarbonyl chloride (0.558ml) there was prepared cyclopropanecarboxylic acid [3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (76mg) as an off-white solid. LC-MS (Method L): $R_T = 5.25$ minutes, 298.26 (M+H)⁺.

- (p) Cyclopropanecarboxylic acid [3-(5-ethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



- 10 By proceeding in a manner similar to Example 248(o) above but using 3-(5-ethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [187mg, Example 233(g)] there was prepared cyclopropanecarboxylic acid [3-(5-ethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (112mg) as a pale yellow solid. LC-MS (Method H): $R_T = 2.26$ minutes, 312.23 (M+H)⁺, 310.30 (M-H)⁻.

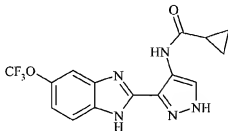
- 15 (q) Cyclopropanecarboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



- By proceeding in a manner similar to Example 248(a) above but using 3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [Example 233(h)] and cyclopropanecarbonyl chloride there

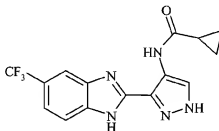
was prepared cyclopropanecarboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (135mg) as a white solid. LC-MS (METHOD M): $R_T = 11.31$ minutes, 300.31 (M+H)⁺.

- (r) Cyclopropanecarboxylic acid [3-(5-trifluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



- By proceeding in a manner similar to Example 248(a) above but using 3-(5-trifluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [Example 233(i)] and cyclopropanecarbonyl chloride there was prepared cyclopropanecarboxylic acid [3-(5-trifluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (275mg) as a white solid. LC-MS (METHOD M): $R_T = 13.57$ minutes, 352.22 (M+H)⁺.

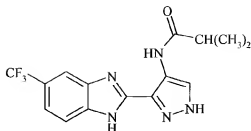
- (s) Cyclopropanecarboxylic acid [3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



- By proceeding in a manner similar to Example 248(a) above but using 3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [Example 233(j)] and cyclopropanecarbonyl chloride there was prepared cyclopropanecarboxylic acid [3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (88mg) as a white solid. LC-MS (METHOD M): $R_T = 13.62$ minutes, 338.12 (M+H)⁺.

- (t) N-[3-(5-Trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isobutyramide

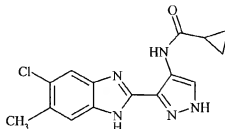
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By proceeding in a manner similar to Example 248(s) above but using isobutyryl chloride there was prepared N-[3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isobutyramide (71mg) as a white solid. LC-MS (METHOD M): $R_T = 10.11$ minutes, 336.12 ($M+H$) $^+$.

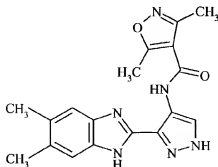
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- (u) Cyclopropanecarboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



- By proceeding in a manner similar to Example 248(a) above but using 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [Example 261] and cyclopropanecarbonyl chloride there was prepared cyclopropanecarboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (46mg) as a white solid. LC-MS (METHOD L): $R_T = 7.06$ minutes, MS: 316.26 ($M+H$) $^+$.

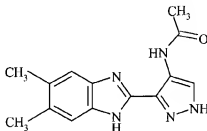
- 15 (v) 3,5-Dimethyl-isoxazole-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



By proceeding in a manner similar to Example 248(a) above but using 3,5-dimethylisoxazole-4-carbonyl chloride there was prepared 3,5-dimethyl-isoxazole-4-carboxylic acid [3-(5,6-dimethyl-1H-

benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (62mg) as a white solid. LC-MS (METHOD L): $R_T = 8.45$ minutes, 351.32 (M+H)⁺.

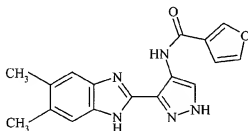
(w) N-[3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide



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By proceeding in a manner similar to Example 248(a) above but using acetyl chloride there was prepared N-[3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide (25mg) as a white solid. LC-MS (METHOD L): $R_T = 6.34$ minutes, 270.14 (M+H)⁺.

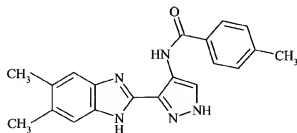
10 (x) Furan-3-carboxylic acid [3-(5,6-dimethylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide



By proceeding in a manner similar to Example 248 (a) above but using 3-furoylchloride there was prepared furan-3-carboxylic acid [3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide

15 (80mg) as a white solid. LC-MS (METHOD L): $R_T = 7.10$ minutes, 322.31 (M+H)⁺.

(y) N-[3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-4-methyl-benzamide

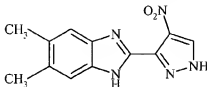


By proceeding in a manner similar to Example 248(a) above but using *p*-toluoyl chloride there was prepared N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-4-methyl-benzamide (42mg) as a white solid. LC-MS (METHOD L): $R_T = 12.24$ minutes, 346 (M+H)⁺.

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EXAMPLE 249

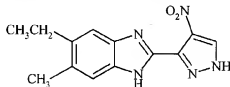
(a) 5,6-Dimethyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole



A stirred solution of 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4,5-dimethylphenyl)amide [5.7g, Reference Example 36(a)] in acetic acid (100mL) was heated at 120°C for 1 hour, then cooled to ambient temperature and then evaporated. The oily residue was partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate and then evaporated to give 5,6-dimethyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole (5.70 g) as an orange solid. LC-MS (METHOD B): $R_T = 2.30$ minutes, 258.11 (M+H)⁺.

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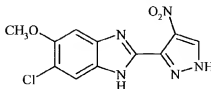
(b) 5-Ethyl-6-methyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole



By proceeding in a manner similar to Example 249(a) above but using 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-ethyl-5-methylphenyl)amide [Reference Example 36(b)] there was prepared 5-ethyl-6-methyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole as a yellow solid. LC-MS (METHOD B): $R_T = 2.61$ minutes, 272.23 (M+H)⁺.

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(c) 6-Chloro-5-methoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole



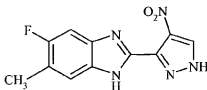
By proceeding in a manner similar to Example 249(a) above but using 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-5-chloro-4-methoxyphenyl)amide [1.5g, Reference Example 36(c)] there was

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-430-

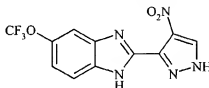
prepared 6-chloro-5-methoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole (0.7g) as a dark solid.
MS: 294 (M+H)⁺.

(d) 5-Fluoro-6-methyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole



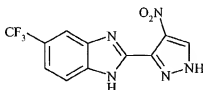
By proceeding in a manner similar to Example 249(a) above but using 4-Nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-fluoro-5-methyl-phenyl)-amide [Reference Example 36(f)] there was prepared 5-fluoro-6-methyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole (0.730g) as a red solid.
LC-MS (METHOD J): R_T = 2.76 minutes, 262.21 (M+H)⁺.

(e) 2-(4-Nitro-1H-pyrazol-3-yl)-5-trifluoromethoxy-1H-benzimidazole



By proceeding in a manner similar to Example 249(a) above but using 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-trifluoromethoxy-phenyl)-amide [Reference Example 36(g)] there was prepared 2-(4-nitro-1H-pyrazol-3-yl)-5-trifluoromethoxy-1H-benzimidazole (1.02g) as a red solid.
LC-MS (METHOD J): R_T = 3.32 minutes, 314.19 (M+H)⁺.

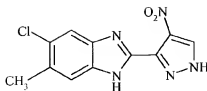
(f) 2-(4-Nitro-1H-pyrazol-3-yl)-5-trifluoromethyl-1H-benzimidazole



By proceeding in a manner similar to Example 249(a) above but using 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-trifluoromethyl-phenyl)-amide [Reference Example 36(h)] there was prepared 2-(4-nitro-1H-pyrazol-3-yl)-5-trifluoromethyl-1H-benzimidazole (0.195g) as an orange solid.
MS: 298.07 (M+H)⁺. HPLC (METHOD B): R_T = 3.50 minutes.

(g) 5-Chloro-6-methyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole

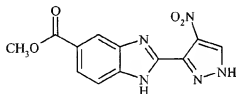
-431-



By proceeding in a manner similar to Example 249(a) above but using 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-chloro-5-methyl-phenyl)-amide [Reference Example 36(i)] there was prepared 5-chloro-6-methyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole (0.320g) as an orange

- 5 solid. LC-MS (METHOD C): $R_T = 3.36$ minutes, 314.19 (M+H)⁺.

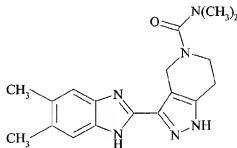
(h) 2-(4-Nitro-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid methyl ester



- 10 By proceeding in a manner similar to Example 249(a) above but using 3-amino-4-[(4-nitro-1H-pyrazole-3-carbonyl)-amino]-benzoic acid methyl ester [Reference Example 36(j)] there was prepared 2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid methyl ester (2.50g) as a yellow solid. LC-MS (METHOD B): $R_T = 2.76$ minutes, 288.12 (M+H)⁺.

EXAMPLE 250

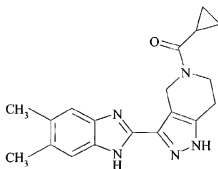
- 15 (a) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid isopropylamide



- 20 A solution of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine [0.150g, Example 251(a)] in dimethyl formamide (4ml) was treated with diisopropylethylamine (0.54ml) and then with dimethyl carbamyl chloride (0.122ml). After stirring for 1 hour the reaction mixture was quenched by the addition of methanol (0.1ml) and then diluted with ethyl acetate. This mixture was washed five times with brine and then evaporated. The residue was treated with tetrahydrofuran (9ml) and methanol (3ml) and the resulting solution was then treated with potassium

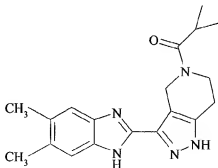
hydroxide (50mg). This mixture was stirred for 1 hour, then acidified by addition of hydrochloric acid (1M) and then extracted three times with ethyl acetate. The aqueous layer was basified by addition of sodium carbonate and the resulting suspension was filtered, then washed with water, then dried in air and then azeotroped with toluene to yield 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid isopropylamide as a pale brown solid. MS: 339 (M+H)⁺. HPLC (METHOD F1): R_T = 8.67 minutes.

- (b) Cyclopropyl-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-methanone



By proceeding in a manner similar to Example 250(a) above, but using cyclopropanecarbonylchloride and stirring the reaction mixture for 16 hours, there was prepared cyclopropyl-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-methanone (68mg) as a pale yellow solid. LC-MS (METHOD M): R_T = 10.57 minutes, 336 (M+H)⁺.

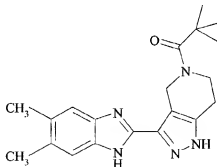
- (c) Isopropyl-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-methanone



By proceeding in a manner similar to Example 250(b) above, but using isopropylcarbonyl chloride, cyclopropylcarbonylchloride there was prepared isopropyl-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-

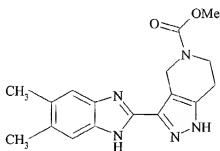
1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-methanone (68mg) as a white solid. LC-MS (METHOD M): $R_T = 9.28$ minutes, 338 (M+H)⁺.

(d) 1-[3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-2,2-dimethyl-propan-1-one



By proceeding in a manner similar to Example 250(b) above, but using trimethylacetyl chloride and filtering the precipitate formed upon basification with sodium carbonate, followed by azeotrope with toluene there was prepared 1-[3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-2,2-dimethyl-propan-1-one (49mg) as a pale yellow solid. LC-MS (METHOD M): $R_T = 11.39$ minutes, 352 (M+H)⁺.

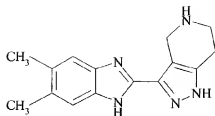
(e) 3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid methyl ester



By proceeding in a manner similar to Example 250(b) above but using methylchloroformate there was prepared 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid methyl ester (89mg) as a pale brown solid. LC-MS (METHOD M): $R_T = 8.95$ minutes, 326 (M+H)⁺.

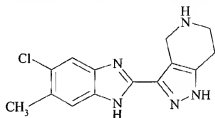
EXAMPLE 251

(a) 3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine



- A solution of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester [1.014g, Example 252(a)] in methanol (20ml) was treated with a solution of hydrogen chloride in dioxane (5ml, 4M). After stirring for 16 hours the reaction mixture was evaporated. The resulting beige solid was triturated with methanol to yield 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (0.523g) as a pale yellow solid.
- LC-MS (METHOD B): $R_T = 0.63$ minutes; 268 (M+H)⁺.

- (b) 3-(5-Chloro-6-methyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine

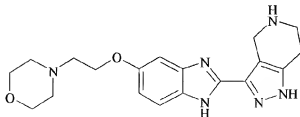


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By proceeding in a manner similar to Example 251(a) above, but using 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester [Example 252(d)] there was prepared 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (223mg) as a white solid. LC-MS (METHOD K): $R_T = 3.91$ minutes,

15 288/290 (M+H)⁺.

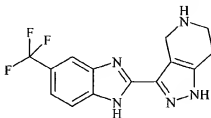
- (c) 3-[5-(2-Morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine



- 20 By proceeding in a manner similar to Example 251(a) above, but using 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester [Example 252(e)] there was prepared 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-4,5,6,7-

tetrahydro-1H-pyrazolo[4,3-c]pyridine (200mg) as an off-white solid. LC-MS (METHOD N): $R_T = 2.55$ minutes, 369.19 (M+H)⁺.

(d) 3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine



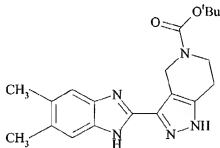
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By proceeding in a manner similar to Example 251(a) above but using 3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester [Example 252(g)] there was prepared 3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (500mg) as an off-white solid. LC-MS (METHOD N): $R_T = 3.21$ minutes, 308.17 (M+H)⁺.

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EXAMPLE 252

(a) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester



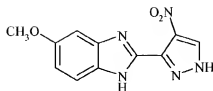
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A suspension of 1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-3,5-dicarboxylic acid, 3-(2-amino-4,5-dimethylphenyl)amide, 5-*tert*-butyl ester [1.091g, Reference Example 39(a)] in acetic acid (5ml) was heated to 100°C for 12 minutes in a Smith Creator Microwave. The mixture was neutralised with care by addition of solid sodium hydrogen carbonate and then extracted twice with ethyl acetate. The combined extracts were evaporated to yield 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester. LC-MS (METHOD B): $R_T = 2.79$ minutes; 368 (M+H)⁺.

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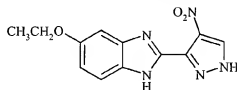
(b) 5-Methoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole

-436-



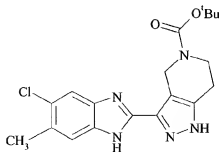
- By proceeding in a manner similar to Example 252(a) above but (i) using 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-methoxy-phenyl)-amide [410mg, Reference Example 36(d)] and heating at 120°C for 5 minutes, (ii) pouring the reaction mixture into water, adjusting to pH14 with 2N sodium hydroxide and filtering, and (iii) adjusting the pH of the filtrate to 6 with 2N hydrochloric acid and collecting the precipitate by filtration, there was prepared 5-methoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole (327mg) as a yellow powder. LC-MS (Method H): $R_T = 1.61$ minutes, 260.25 (M+H)⁺, 258.26 (M-H)⁻.

- 10 (c) 5-Ethoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole



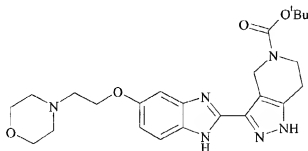
- By proceeding in a manner similar to Example 252(b) above but using 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-ethoxy-phenyl)-amide [824mg, Reference Example 36(e)] there was prepared 5-ethoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole (407mg) as a light brown powder.
- 15 LC-MS (Method H): $R_T = 1.82$ minutes, 274.26 (M+H)⁺, 272.30 (M-H)⁻.

- (d) 3-(5-Chloro-6-methyl-1H-benzoimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester



By proceeding in a manner similar to Example 252(b) above, but using 3-(2-amino-4-chloro-5-methyl-phenylcarbamoyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester [Reference Example 39(c)] and heating at 110°C for 15 minutes, there was prepared 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (391mg) as a brown solid. LC-MS (METHOD J): $R_T = 3.53$ minutes, 388 (M+H)⁺.

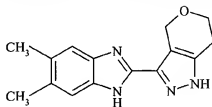
- (e) 3-[5-(2-Morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester



- 10 By proceeding in a manner similar to Example 252(b) above, but using 3-[2-amino-4-(2-morpholin-4-yl-ethoxy)-phenylcarbamoyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester [Reference Example 39(d)] there was prepared 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (350mg) as a brown solid. LC-MS (METHOD N): $R_T = 3.53$ minutes, 469.24 (M+H)⁺.

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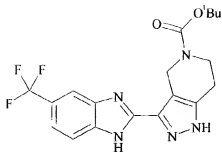
- (f) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyranol[4,3-c]pyrazole



- By proceeding in a manner similar to Example 252(a) above but using 1,4,6,7-tetrahydro-pyranol[4,3-c]pyrazole-3-carboxylic acid (2-amino-4,5-dimethyl-phenyl)-amide [Reference Example 39(e)] and heating at 120°C for 3 minutes there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyranol[4,3-c]pyrazole (49mg) as a pale brown solid. MS: 269 (M+H)⁺. HPLC (METHOD C1): $R_T = 19.68$ minutes.

- 25 (g) 3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

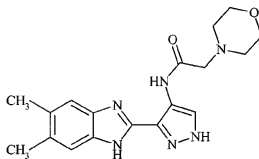
-438-



- By proceeding in a manner similar to Example 252(a) above but using 3-(2-amino-4-trifluoromethyl-phenylcarbamoyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester [Reference Example 39(f)] there was prepared 3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (950mg) was prepared as a brown solid. LC-MS (METHOD N): $R_T = 3.90$ minutes, 408 (M+H)⁺.

EXAMPLE 253

- (a) N-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-morpholin-4-yl-acetamide



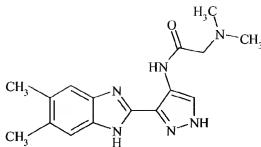
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- A stirred solution of 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [100mg, Example 233(c)] and diisopropylethylamine (307μl) in dichloromethane (10ml) was treated with chloroacetyl chloride (105μl). The reaction mixture was stirred for 30 minutes at room temperature, then treated with morpholine (575μl), then kept at room temperature overnight and then evaporated. The oily residue was partitioned between ethyl acetate and water and the organic phase was washed with water, then dried over magnesium sulfate and then evaporated. The residue was subjected to flash chromatography on silica eluting with ethyl acetate to give the N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-morpholin-4-yl-acetamide (49.9mg) as an off-white solid. MS: 355.68 (M+H)⁺. HPLC (METHOD B1): $R_T = 8.28$ minutes.

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- (b) 2-Dimethylamino-N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide

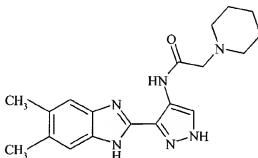
-439-



By proceeding in a manner similar to Example 253(a) above but using dimethylamine hydrochloride there was prepared 2-dimethylamino-N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide (52mg) as a white solid. LC-MS (METHOD M): $R_T = 8.28$ minutes, 355.68 ($M+H$) $^+$.

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(c) N-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-piperidin-1-yl-acetamide

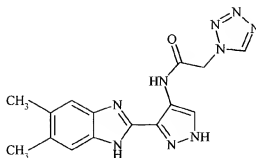


By proceeding in a manner similar to Example 253(a) above but using piperidine there was prepared N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-piperidin-1-yl-acetamide (4mg) as a white solid. LC-MS (METHOD M): $R_T = 7.69$ minutes, 353.68 ($M+H$) $^+$.

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EXAMPLE 254

(a) N-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(1H-1,2,3,4-tetraazol-1-yl)-acetamide

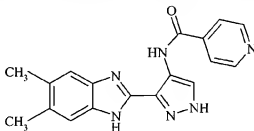


15

A stirred solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (295.7 mg) and diisopropylethylamine (269 μ l) in dimethylformamide (10ml) were treated with 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [100mg, Example 233(c)] and 2-(1H-1,2,3,4-tetraazol-1-yl)

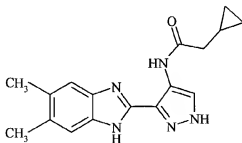
- acetic acid (197.8mg). The reaction mixture was stirred for 72 hours then treated further with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (295.7mg), diisopropylethylamine (269 μ l) and 2-(1H-1,2,3,4-tetraazol-1-yl) acetic acid (197.8mg). Stirring was continued for a further 48 hours then the reaction mixture was partitioned between ethyl acetate and water. The organic phase
- 5 was evaporated and the residue was treated with 1N potassium hydroxide in a mixture of methanol and tetrahydrofuran (1:4, 8 ml). After 1 hour this mixture was extracted with ethyl acetate. The extract was washed with brine, then dried over magnesium sulfate and then evaporated to dryness. The residue was subjected to preparative HPLC to give N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(1H-1,2,3,4-tetraazol-1-yl)-acetamide (13.7mg) as an off-white solid. MS: 338.14 (M+H)⁺.
- 10 HPLC (METHOD B1): R_T = 7.26 minutes.

(b) N-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isonicotinamide



- By proceeding in a manner similar to Example 254(a) above but using isonicotinic acid there was
- 15 prepared N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isonicotinamide (9mg) as a white solid. LC-MS (METHOD L): R_T = 8.71 minutes, 331.21 (M+H)⁺.

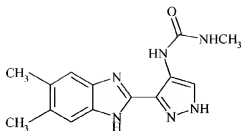
(c) 2-Cyclopropyl-N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide



- By proceeding in a manner similar to Example 254(a) above but using cyclopropylacetic acid there was
- 20 prepared 2-cyclopropyl-N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide (98mg) as a light pink solid. LC-MS (METHOD M): R_T = 11.04 minutes, MS: 310 (M+H)⁺.

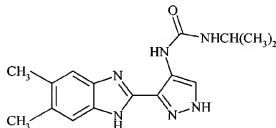
EXAMPLE 255

- (a) 1-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea



- A solution of 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine [0.500g, Example 233(c)] in tetrahydrofuran (5ml) was treated with methyl isocyanate (0.502ml) and the mixture stirred at ambient temperature for 16 hours. The mixture was then concentrated in vacuo and the residue was
- 5 redissolved in 1N potassium hydroxide in a mixture of methanol and tetrahydrofuran (1:3, 5ml). The mixture was stirred for a further 1 hour, then concentrated and then partitioned between ethyl acetate and water. The aqueous layer was extracted three times with ethyl acetate and the combined organic extracts were washed with brine, then dried over magnesium sulfate, and then evaporated. The residue was subjected to flash column chromatography on silica eluting initially with a mixture of ethyl acetate
- 10 and hexane (1:1, v/v) and then with ethyl acetate to afford 1-[3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea (230mg) as a white solid. MS: 269 (M+H)⁺. HPLC (METHOD D1): R_T = 5.97 minutes.

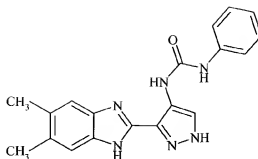
- (b) 1-[3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-isopropyl-urea



15

By proceeding in a manner similar to Example 255(a) above but using isopropyl isocyanate there was prepared 1-[3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-isopropyl-urea as a white solid. MS: 313 (M+H)⁺. HPLC (METHOD D1): R_T = 10.94 minutes.

- 20 (c) 1-[3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-phenyl-urea

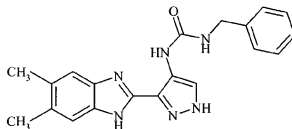


By proceeding in a manner similar to Example 255(a) above but using phenyl isocyanate there was prepared 1-[3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-phenyl-urea as a white solid.

MS: 347 (M+H)⁺. HPLC (METHOD B1): R_T = 16.16 minutes.

5

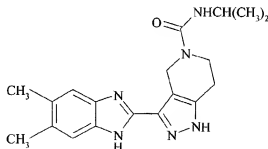
(d) 1-Benzyl-3-[3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea



By proceeding in a manner similar to Example 255(a) above but using benzyl isocyanate there was prepared 1-benzyl-3-[3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea as a white solid.

10 MS: 361(M+H)⁺. HPLC (METHOD D1): R_T = 7.78 minutes.

(e) 3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid isopropylamide

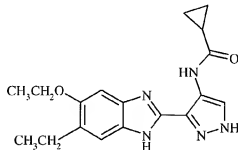


15 By proceeding in a manner similar to Example 255(a) above but using 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine [Example 251(a)] and isopropylisocyanate, and subjecting the reaction product to flash column chromatography eluting with ethyl acetate/methanol (19:1, v/v), there was prepared 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1,4,6,7-

tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid isopropylamide (93.3mg) as an off-white solid. LC-MS (METHOD M): $R_T = 10.15$ minutes, 353 (M+H)⁺.

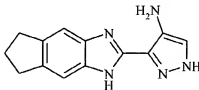
EXAMPLE 256

- 5 (a) Cyclopropanecarboxylic acid[3-(5-ethoxy-6-ethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]amide



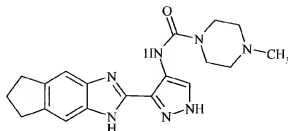
- A solution of cyclopropanecarboxylic acid [3-(5-ethoxy-6-ethyl-1H-benzoimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide [0.3g, Reference Example 48(a)] and p-toluenesulfonic acid hydrate (1.2g) in ethanol (25mL) was heated in an 80°C in an oil bath for 1 hour, then cooled, and then poured into aqueous sodium bicarbonate solution. The aqueous mixture was extracted twice with ethyl acetate (75mL). The combined extracts were evaporated and the residue was redissolved in a mixture of methylene chloride (100mL) and methanol (10mL). This solution was washed with aqueous sodium bicarbonate, to remove some residual p-toluenesulfonic acid, then evaporated to give
- 15 cyclopropanecarboxylic acid[3-(5-ethoxy-6-ethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]amide (120mg) as a white solid. LC-MS (Method E): $R_T = 2.36$ minutes, 340 (M+H)⁺.

- (b) 3-(1,5,6,7-Tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-ylamine



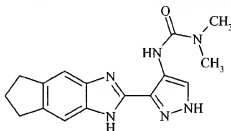
- 20 By proceeding in a similar manner to Example 256(a) but using 3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-ylamine [0.9g, Reference Example 49(d)] and p-toluenesulfonic acid (1.0g) in ethanol (100 mL) and carrying out the reaction at 55°C for 2 hours, there was prepared 3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-ylamine (800 mg) as a brown solid. LC-MS (Method G): $R_T = 2.68$ minutes, 240 (M+H)⁺.

(c) 4-Methylpiperazine-1-carboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]amide



- By proceeding in a similar manner to Example 256(a) but (i) using 4-methylpiperazine-1-carboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide [171 mg, Reference Example 48(b)], (ii) carrying out the reaction at 55°C for 1.5 hours, then at 70°C for 1 hour, and (iii) subjecting the reaction product to chromatography on silica gel (ethyl acetate/gradient 0 to 20% methanol), there was prepared 4-methylpiperazine-1-carboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]amide (55 mg) as a white solid. LC-MS (Method E): $R_T = 1.53$ minutes, 366 (M+H)⁺.

(d) 1,1-Dimethyl-3-[3-(1,5,6,7-tetrahydro-s-indacen-2-yl)-1H-pyrazol-4-yl]urea

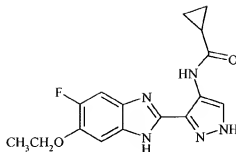


- By proceeding in a similar manner to Example 256(c) but using 1,1-dimethyl-3-[3-(1,5,6,7-tetrahydro-s-indacen-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]urea (230mg) and p-toluenesulfonic acid hydrate [40 mg, Reference Example 48(c)] there was prepared 1,1-dimethyl-3-[3-(1,5,6,7-tetrahydro-s-indacen-2-yl)-1H-pyrazol-4-yl]urea (106 mg) as a tan solid. LC-MS (Method E): $R_T = 1.97$ minutes, 311 (M+H)⁺.

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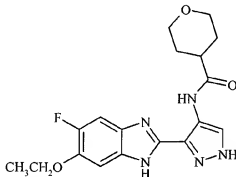
EXAMPLE 257

(a) Cyclopropanecarboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide



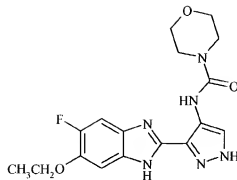
- A solution of cyclopropanecarboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide [90mg, Reference Example 48(d)] in a 1/1 mixture of trifluoroacetic acid and dichloromethane (30mL) was stirred for 5 hours and then evaporated. The residue was mixed with ethyl acetate (30mL) and aqueous sodium bicarbonate (30mL). The organic layer was evaporated to give cyclopropanecarboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide (44 mg). LC-MS (Method E): $R_T = 2.34$ minutes, 330 (M+H)⁺.

- (b) Tetrahydropyran-4-carboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazole-4-yl]amide



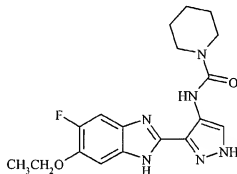
- By proceeding in a similar manner to Example 257(a) but using tetrahydropyran-4-carboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazole-4-yl]amide [120 mg, Reference Example 48(e)] there was prepared tetrahydropyran-4-carboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazole-4-yl]amide (65mg). LC-MS (Method E) $R_T = 2.17$ minutes, 374 (M+H)⁺.

- (c) Morpholine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide



- By proceeding in a similar manner to Example 257(a) but using morpholine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide [140mg, Reference Example 48(f)] there was prepared morpholine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide (65mg). LC-MS (Method E): $R_T = 2.62$ minutes, 375 (M+H)⁺.

- (d) Piperidine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide



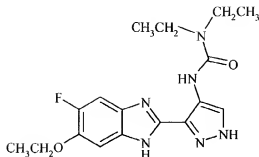
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By proceeding in a similar manner to Example 257(a) but using piperidine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide [127mg, Reference Example 48(g)] there was prepared piperidine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide (65mg). LC-MS (Method E): $R_T = 3.15$ minutes. MS 373

15 (M+H)⁺.

- (e) 3-[6-Ethoxy-5-fluoro-1H-benzimidazol-2-yl]-1H-pyrazol-4-yl]-1,1-diethylurea

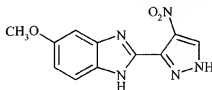
-447-



By proceeding in a similar manner to Example 257(a) but using 3-[6-ethoxy-5-fluoro-1H-benzimidazol-2-yl]-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]-1,1-diethylurea (110 mg, Reference Example 48(h)) there was prepared 3-[6-ethoxy-5-fluoro-1H-benzimidazol-2-yl]-1H-pyrazol-4-yl]-1,1-diethylurea

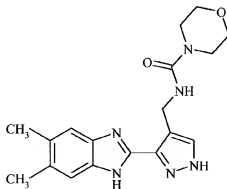
- 5 (65mg). LC-MS (Method E): R_T = 3.13 minutes, 361 (M+H)⁺.

(f) 5-Methoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole



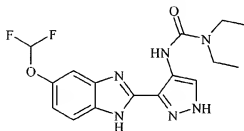
- 10 By proceeding in a similar manner to Example 257(a) but using 5-methoxy-2-[4-nitro-1-(tetrahydropyran-2-yl)-1H-pyrazol-3-yl]-1H-benzimidazole (282mg, Reference Example 50(d)) there was prepared 5-methoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole (373mg) as a red powder. LC-MS (Method H): R_T = 1.60 minutes, 260.22 (M+H)⁺, 258.23 (M-H)⁻.

- 15 (g) Morpholine-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylmethyl]-amide



- By proceeding in a similar manner to Example 257(a) but using morpholine-4-carboxylic acid (2,4-dimethoxy-benzyl)-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-ylmethyl]-amide (Reference Example 59), subjecting the reaction product to flash chromatography on silica [eluting with dichloromethane to dichloromethane/methanol (9:1)] and recrystallising from water/acetonitrile followed by titration with diethyl ether there was prepared morpholine-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylmethyl]-amide (16.5mg) as a white solid. LC-MS (Method M): $R_T = 6.97$ minutes, MS: 355.36 (M+H)⁺, 353.39 (M-H)⁻.

- (h) 3-[3-(5-Difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea

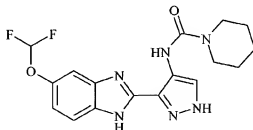


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By proceeding in a manner similar to Example 257(a) above but using 3-[3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea [Reference Example 48(j)] there was prepared 3-[3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea (60mg) as a white solid. LC-MS (METHOD L): $R_T = 10.61$ minutes.

- 15 ¹H NMR(CD₃OD): δ 1.24 (t, 6H), 3.43 (q, 4H), 6.72 (bt, 1H), 6.98 (d, 1H), 7.26 (s, 1H), 7.47 (d, 1H), 7.91 (s, 1H).

- (i) Piperidine-1-carboxylic acid [3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



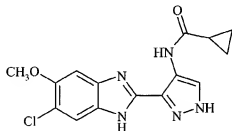
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By proceeding in a manner similar to Example 257(a) above but using piperidine-1-carboxylic acid [3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-yl]-amide [Reference Example 48(k)], there was prepared piperidine-1-carboxylic acid [3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (52mg) as a white solid. HPLC (METHOD E1): R_T

= 10.78 minutes. ^1H NMR(CD_3OD): δ 1.69 (bm, 6H), 3.64 (bm, 4H), 6.82 (bt, 1H), 7.09 (bm, 1H), 7.39 (bm, 1H), 7.61 (bm, 1H), 8.05 (bm, 1H).

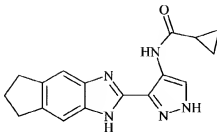
EXAMPLE 258

- 5 (a) Cyclopropanecarboxylic acid [3-(6-chloro-5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide



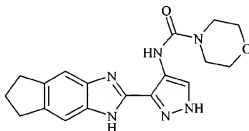
- A solution of 3-(6-chloro-5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine [50mg, Example 233(e)] and diisopropylethylamine (40 μL) in dichloromethane (20mL), stirred at room temperature, was treated with cyclopropanecarbonyl chloride (51 μL , 3 eq). After stirring for a further 20 hours the reaction mixture was evaporated and the residue was subjected to chromatography on silica gel (ethyl acetate/heptane 1/1) to give the bis-acylated product (60mg) as an orange solid. MS 400 ($\text{M}+\text{H}$) $^+$. The bis-acylated product was dissolved in methanol (5 mL), then treated with potassium hydroxide solution (0.5mL, 5N), then stirred at 60°C for 1 hour, then cooled and then evaporated. The residue was treated with water (15mL) and the pH of the aqueous mixture was adjusted to 5 and then extracted twice with ethyl acetate (25mL). The combined extracts were dried with magnesium sulfate, then evaporated and the residue was triturated with diisopropyl ether, filtered and the precipitate was vacuum dried at 60°C to give cyclopropanecarboxylic acid [3-(6-chloro-5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (11 mg) as an off-white solid, mp 225-226°C. LC-MS (Method E): R_T = 2.92 minutes, 332 ($\text{M}+\text{H}$) $^+$.
- 10
- 15
- 20

- (b) Cyclopropanecarboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]amide

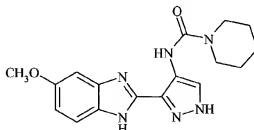


- By proceeding in a similar manner to Example 258(a) above but (i) treating a solution of 3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-ylamine [310 mg, Example 256(b)] and triethylamine (4 eq) in tetrahydrofuran (15 mL) with cyclopropanecarbonyl chloride (4 eq), (ii) stirring the reaction mixture at 60°C for 2 hours, (iii) treating the resulting bis-acylated product with
- 5 methanolic potassium hydroxide (20 mL, 1.05g KOH) at 40°C for 1 hour followed by treatment with aqueous ammonium chloride (200 mL), (iii) extracting this mixture three times with ethyl acetate (100mL), (iv) evaporating the combined extracts and (v) chromatographing the residue on silica gel (ethyl acetate / gradient of 50-0% heptane) there was prepared cyclopropanecarboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]amide (50mg) as a yellow solid. LC-MS
- 10 (Method E) $R_T = 2.05$ minutes, 308 (M+H)⁺.

(c) Morpholine-4-carboxylic acid[3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]-amide



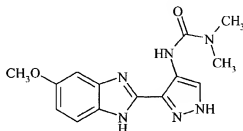
- 15 By proceeding in a similar manner to Example 258(b) above but using morpholine-4-carbonyl chloride there was prepared morpholine-4-carboxylic acid[3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]-amide as an orange solid. LC-MS (Method E) $R_T = 2.45$ minutes, 353 (M+H)⁺.
- 20 (d) Piperidine-1-carboxylic acid [3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



By proceeding in a similar manner to Example 258(a) above treating 3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [257mg, Example 233(f)] with 1-piperidine-carbonyl chloride in the presence of diisopropylethylamine and using tetrahydrofuran as the solvent there was prepared

piperidine-1-carboxylic acid [3-(5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (46.1 mg) as a white solid. LC-MS (Method L) R_T = 6.43 minutes, 341.28 (M+H)⁺.

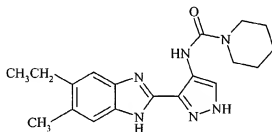
(e) 3-[3-(5-Methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea



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By proceeding in a manner similar to Example 258(d) above but using dimethylcarbonyl chloride there was prepared 3-[3-(5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea as a white solid. LC-MS (Method M): R_T = 7.64 minutes, 301.35 (M+H)⁺.

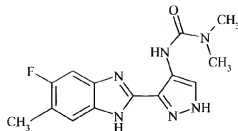
10 (f) Piperidine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide



15 By proceeding in a manner similar to Example 258(d) above but (i) using 3-(5-ethyl-6-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine [400mg, Example 233(d)], 1-piperidinecarbonyl chloride (1.25ml) and diisopropylethylamine (1.74ml) with tetrahydrofuran (20ml) as the solvent and, stirring the reaction mixture at ambient temperature for 48 hours, then at 50°C for 24 hours, (ii) treating the bis-acylated product with 1M potassium hydroxide in methanol/tetrahydrofuran (1:3, 20ml) at room temperature, and (iii) subjecting the product to flash column chromatography on silica [eluting with ethyl acetate/hexane (1:1 v/v) to ethyl acetate/hexane (3:1 v/v)], there was prepared piperidine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (425mg) as a white solid. LC-MS (METHOD L): R_T = 7.55 minutes, 353.34 (M+H)⁺.

20 (g) 3-[3-(5-Fluoro-6-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea

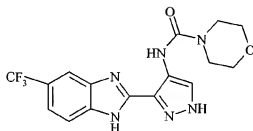
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By proceeding in a manner similar to Example 258(f) above but using 3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [Example 233(h)] and *N,N'*-dimethylcarbonylchloride there was prepared 3-[3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-

- 5 urea (32mg) as a white solid. LC-MS (METHOD M): $R_T = 10.40$ minutes, 303.34 ($M+H$)⁺.

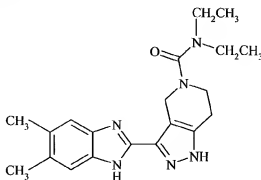
- (h) Morpholine-4-carboxylic acid [3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-
amide



- 10 By proceeding in a manner similar to Example 258(f) above but using 3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [Example 233(j)] and morpholine-1-carbonyl chloride there was prepared morpholine-4-carboxylic acid [3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-
4-yl]-amide (131mg) was prepared as a white solid. MS: 379.08 ($M-H$)⁻. HPLC (METHOD E1): $R_T =$
10.61 minutes.

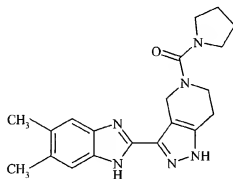
15

- (i) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-
carboxylic acid diethylamide



- By proceeding in a manner similar to Example 258(f) above, but using 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine [Example 251(a)] and diethylcarbonyl chloride, and subjecting the reaction product to flash column chromatography eluting with ethyl acetate to ethyl acetate/methanol (49:1, v/v), there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide (20.9mg) as an off-white solid. LC-MS (METHOD J): $R_T = 3.44$ minutes, 367 (M+H)⁺.

- (j) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-pyrrolidin-1-yl-methanone

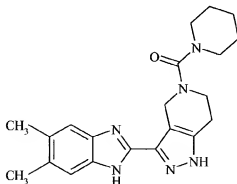


10

By proceeding in a manner similar to Example 258(i) above, but using 1-pyrrolidincarbonyl chloride and triturating the reaction product with ethyl acetate, methanol and dichloromethane, there was prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-pyrrolidin-1-yl-methanone (68mg) as an off-white solid. MS: 365 (M+H)⁺. HPLC (METHOD E1):

15 $R_T = 10.32$ minutes.

- (k) 3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-piperidin-1-yl-methanone

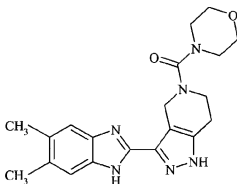


- 20 By proceeding in a manner similar to Example 258(f) above, but using 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine [Example 251(a)] and subjecting

the reaction product to flash column chromatography eluting with ethyl acetate/petrol (5:1, v/v) to 100% ethyl acetate to ethyl acetate/methanol (19:1, v/v), there was prepared 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-piperidin-1-yl-methanone (93.3mg) as an off-white solid. LC-MS (METHOD L): $R_T = 6.77$ minutes, 379 (M+H)⁺.

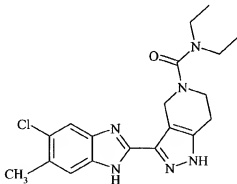
5

- (l) 3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-morpholin-4-yl-methanone



- By proceeding in a manner similar to Example 258(k) above, but using 1-morpholinecarbonyl chloride and azeotroping the reaction product with toluene and dichloromethane, there was prepared 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-morpholin-4-yl-methanone (32mg) as an off-white solid. MS: 381 (M+H)⁺. HPLC (METHOD E1): $R_T = 9.39$ minutes.

- (m) 3-(5-Chloro-6-methyl-1H-benzoimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide

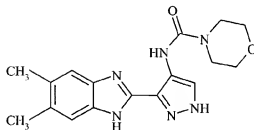


- By proceeding in a manner similar to Example 258(a) above but (i) using 3-(5-chloro-6-methyl-1H-benzoimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine [Example 251(b)] and diethylcarbonyl chloride, and (ii) subjecting the reaction product to flash column chromatography, eluting with ethyl acetate to ethyl acetate/methanol (47:3, v/v) followed by trituration with ethanol,

20

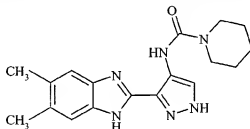
there was prepared 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide (35.6mg) as a pale yellow solid. MS: 387/389 (M+H)⁺. HPLC (METHOD E1): R_T = 11.07 minutes.

- 5 (n) Morpholine-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



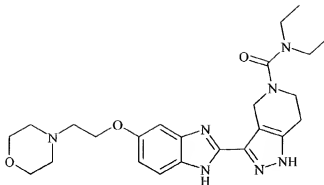
- By proceeding in a manner similar to Example 258(p) above but using 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [Example 233(c)] and 1-morpholinecarbonyl chloride there was prepared morpholine-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (206mg) as a white solid. LC-MS (METHOD L): R_T = 7.36 minutes, 341 (M+H)⁺.
- 10

- (o) Piperidine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



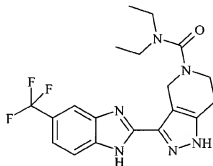
- By proceeding in a manner similar to Example 258(p) above but using 1-piperidinecarbonyl chloride there was prepared piperidine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (185mg) as a white solid. LC-MS (METHOD M): R_T = 10.79 minutes, 339 (M+H)⁺.
- 15

- (p) 3-[5-(2-Morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide
- 20



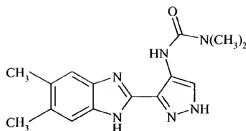
- By proceeding in a manner similar to Example 258(a) above but using 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzoimidazol-2-yl]-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine [Example 251(c)] and diethylcarbonyl chloride there was prepared 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzoimidazol-2-yl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide (28mg) as a white solid. MS: 468.30 (M+H)⁺. HPLC (METHOD E1): R_T = 9.47 minutes.

- (q) 3-(5-trifluoromethyl-1H-benzoimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide



- By proceeding in a manner similar to Example 258(a) above but using 3-(5-trifluoromethyl-1H-benzoimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine [Example 251(d)] and diethylcarbonyl chloride there was prepared 3-(5-trifluoromethyl-1H-benzoimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide (103mg) as a white solid. MS: 407.17 (M+H)⁺. HPLC (METHOD E1): R_T = 10.81 minutes.

- (r) 3-[3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea



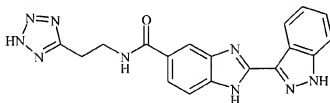
By proceeding in a manner similar to Example 258(p) above but using dimethylcarbamyl chloride there was prepared 3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea. MS:

299 (M+H)⁺. HPLC (Method E1): R_T = 8.24 minutes.

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EXAMPLE 259

2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [2-(2H-tetrazol-5-yl)-ethyl]-amide

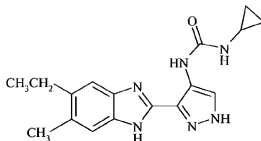


A stirred solution of 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-cyano-ethyl)-amide [150mg, Example 246(s)] and azidotributyltin (2ml) was heated at 95°C for 24 hours. The reaction was cooled to ambient temperature and stirred for 2 hours with acetonitrile (20ml), tetrahydrofuran (10ml) and acetic acid (20ml). The reaction mixture was washed with iso-hexane (6 x 80ml) and concentrated *in vacuo*. The residue was subjected to preparative HPLC to give 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [2-(2H-tetrazol-5-yl)-ethyl]-amide (35.9mg) as a brown solid.

15 LC-MS (Method L): R_T = 9.80 minutes, 374.21 (M+H)⁺.

EXAMPLE 260

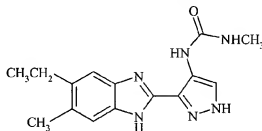
(a) 1-Cyclopropyl-3-[3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea



To a stirred solution of 3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [250mg, Example 233(d)] in tetrahydrofuran (20ml) was added 1,1-carbonyldiimidazole (740mg) and the reaction heated at reflux for 60 hours. The reaction mixture was cooled to ambient temperature and the solvent removed *in vacuo*. The residue was added 2M cyclopropylamine in tetrahydrofuran (15ml).

- 5 The reaction mixture was transferred to a pressure tube and heated at reflux for 48 hours. The reaction mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The aqueous layer was extracted three times with ethyl acetate and the combined organic extracts washed with brine, dried over magnesium sulfate, and concentrated. The residue was subjected to flash column chromatography on silica eluting with ethyl acetate/hexane (1:1 v/v) to 100% ethyl acetate to afford 1-cyclopropyl-3-[3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea (95mg) as a white solid. LC-MS (METHOD M): $R_T = 9.40$ minutes, 325.32 (M+H)⁺.

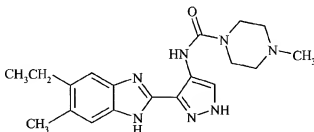
(b) 1-[3-(5-Ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea



- 15 By proceeding in a manner similar to Example 260(a) above but using 2M methylamine in tetrahydrofuran there was prepared 1-[3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea (36mg) as a white solid. LC-MS (METHOD M): $R_T = 7.08$ minutes, 299.34 (M+H)⁺.

(c) 4-Methyl-piperazine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide

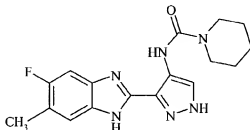
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By proceeding in a manner similar to Example 260(a) above but using 2M 1-methylpiperazine in tetrahydrofuran there was prepared 4-methyl-piperazine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (247mg) as a white solid. LC-MS (METHOD M):

- 25 $R_T = 5.21$ minutes, 368.32 (M+H)⁺.

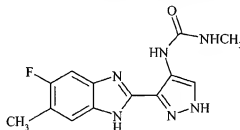
- (d) Piperidine-1-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



- 5 By proceeding in a manner similar to Example 260(a) above but using 3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [Example 233(h)] and 2M piperidine in tetrahydrofuran there was prepared piperidine-1-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (140mg) as a white solid. LC-MS (METHOD L): $R_T = 8.29$ minutes, 343.26 (M+H)⁺.

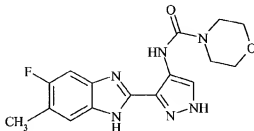
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- (e) 1-[3-(5-Fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea



- By proceeding in a manner similar to Example 260(d) above but using 2M methylamine in tetrahydrofuran there was prepared 1-[3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea (61mg) as a white solid. LC-MS (METHOD L): $R_T = 4.85$ minutes, 289.26 (M+H)⁺.
- 15

- (f) Morpholine-4-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide

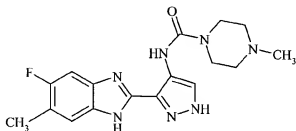


- 20 By proceeding in a manner similar to Example 260(d) above but using 2M morpholine in tetrahydrofuran there was prepared morpholine-4-carboxylic acid [3-(5-fluoro-6-methyl-1H-

-460-

benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (49mg) as a white solid. LC-MS (METHOD L): $R_T = 6.26$ minutes, 345.33 (M+H)⁺.

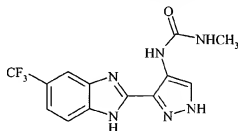
(g) 4-Methyl-piperazine-1-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide



By proceeding in a manner similar to Example 31(d) above but using 2M 1-methylpiperazine in tetrahydrofuran there was prepared 4-methyl-piperazine-1-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (58mg) as a white solid. LC-MS (METHOD P): $R_T =$

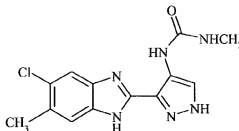
7.72 minutes, 358.19 (M+H)⁺.

(h) 1-Methyl-3-[3-(5-trifluoromethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea



By proceeding in a manner similar to Example 260(a) above but using 3-(5-trifluoromethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine [Example 233(j)] and 2M methylamine in tetrahydrofuran there was prepared 1-methyl-3-[3-(5-trifluoromethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-urea (99mg) as a white solid. LC-MS (METHOD L): $R_T = 6.51$ minutes, 325 (M+H)⁺.

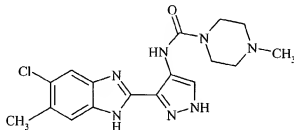
(i) 1-[3-(5-Chloro-6-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea



By proceeding in a manner similar to Example 260(a) above but using 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [Example 261] and 2M methylamine in tetrahydrofuran there was prepared 1-[3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea (45mg) as a white solid. LC-MS (METHOD L): $R_T = 5.85$ minutes, 305/307 (M+H)⁺.

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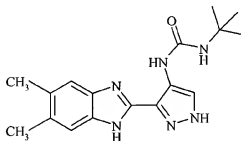
- (j) 4-Methyl-piperazine-1-carboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



- By proceeding in a manner similar to Example 260(i) above but using 2M 1-methylpiperazine in tetrahydrofuran there was prepared 4-methyl-piperazine-1-carboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (60mg) as a pale yellow solid. LC-MS (METHOD M): $R_T = 6.35$ minutes, 374 (M+H)⁺.

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- (k) 1-tert-Butyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea



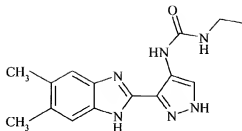
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By proceeding in a manner similar to Example 260(a) above but using 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine [Example 233(c)] and *tert*-butylamine there was prepared 1-tert-butyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea (21mg) as a white solid. LC-MS (METHOD L): $R_T = 5.38$ minutes, 327 (M+H)⁺.

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- (l) 1-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-ethyl-urea

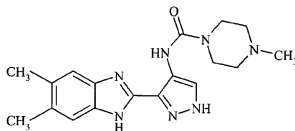
-462-



By proceeding in a manner similar to Example 260(k) above but using 2M ethylamine in tetrahydrofuran there was prepared 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-ethyl-urea (39mg) as a white solid. LC-MS (METHOD L): $R_T = 3.95$ minutes, 299 (M+H)⁺.

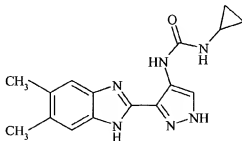
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- (m) 4-Methyl-piperazine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide



- 10 By proceeding in a manner similar to Example 260(k) above but using 2M 1-methylpiperazine in tetrahydrofuran there was prepared 4-methyl-piperazine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide (113mg) as a white solid. MS: 354 (M+H)⁺. HPLC (METHOD E1): $R_T = 10.21$ minutes.

- (n) 1-Cyclopropyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea

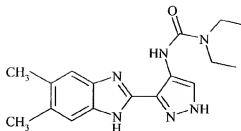


15

By proceeding in a manner similar to Example 260(k) above but using cyclopropylamine there was prepared 1-cyclopropyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea (80mg) as a white solid. MS: 311 (M+H)⁺. HPLC (METHOD E1): $R_T = 10.36$ minutes.

- 20 (o) 3-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea

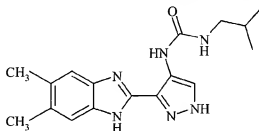
-463-



By proceeding in a manner similar to Example 260(k) above but using 2M diethylamine in tetrahydrofuran there was prepared 3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea (61mg) as a white solid. MS: 327 (M+H)⁺. HPLC (METHOD E1): R_T = 11.36 minutes.

5

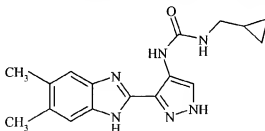
(p) 1-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-isobutyl-urea



By proceeding in a manner similar to Example 260(k) above but using 2M isobutylamine in tetrahydrofuran, there was prepared 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-isobutyl-urea (58mg) as a white solid. MS: 327 (M+H)⁺. HPLC (METHOD E1): R_T = 10.95 minutes.

10

(q) 1-Cyclopropylmethyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea



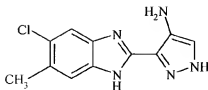
By proceeding in a manner similar to Example 260(k) above but using 2M (aminomethyl)cyclopropane in tetrahydrofuran, there was prepared 1-cyclopropylmethyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea (29mg) as a white solid. MS: 325 (M+H)⁺. HPLC (METHOD E1): R_T = 10.63 minutes.

15

EXAMPLE 261

20 3-(5-Chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine

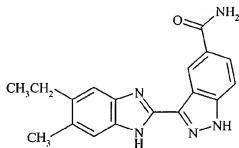
-464-



A stirred solution of 5-chloro-6-methyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole [0.320g, Example 249(g)] and tin chloride (1.10g) in ethanol (5 ml) was heated in a Smith Creator microwave at 140°C for 10 minutes. The reaction mixture was basified using saturated sodium hydrogen carbonate solution to pH 8 and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine as a pale brown solid. LC-MS (METHOD B): $R_T = 2.28$ minutes, 248.13 (M+H)⁺.

EXAMPLE 262

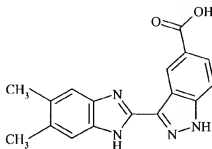
10 3-(5-Ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole-5-carboxylic acid amide dihydrochloride



.2HCl

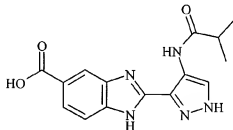
A stirred suspension of 3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole-5-carbonitrile [100mg, Example 235(an)] in acetic acid (1ml) and concentrated hydrochloric acid (1ml) was heated at 80°C for 30 minutes and then at 100°C for 4 hours. The reaction was cooled to ambient temperature and stirred for 16 hours. The reaction was then heated at 80°C for 2.5 hours and then at 100°C for 2 hours. The reaction mixture was cooled to ambient temperature and neutralized with aqueous sodium carbonate solution. The resulting white precipitate was collected by filtration and the aqueous layer was extracted with ethyl acetate, combined with the precipitate and concentrated *in vacuo*. The residue was taken up in methanol, transferred to a solid phase cartridge containing MP-carbonate resin (100mg) and shaken for 16 hours. The reaction was then filtered, the resin washed with methanol and the combined organic layers concentrated *in vacuo*. The residue was triturated with diethyl ether, taken up in methanol and acidified with 4M hydrogen chloride in 1,4-dioxane. The solvent was removed *in vacuo* to give 3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole-5-carboxylic acid amide dihydrochloride (58mg) as a pale brown solid. LC-MS (METHOD M): $R_T = 9.40$ minutes,

25 320(M+H)⁺.

EXAMPLE 2633-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1H-indazole-5-carboxylic acid

A stirred suspension of 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-indazole-5-carbonitrile dihydrochloride [200mg, Reference Example 6(aq)] in acetic acid/concentrated hydrochloric acid (4ml, 1:1 v/v) was heated at 100°C for 16 hours. The reaction mixture was cooled to ambient temperature and filtered. The precipitate was washed with water and dried *in vacuo* to give 3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-indazole-5-carboxylic acid (195mg) as a white solid. LC-MS (METHOD B): $R_T = 2.52$ minutes, 307 (M+H)⁺.

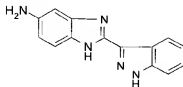
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EXAMPLE 2642-(4-Isobutrylamino-1H-pyrazol-3-yl)-1H-benzoimidazole-5-carboxylic acid

To a stirred solution of 2-(4-amino-1H-pyrazol-3-yl)-1H-benzoimidazole-5-carboxylic acid methyl ester [200mg, Example 233(k)] in tetrahydrofuran (5ml) was added diisopropylethylamine (545μl) and isobutyryl chloride (327μl) dropwise and the reaction stirred for 30 minutes. The reaction mixture was concentrated *in vacuo* and the residue was taken up in 1M potassium hydroxide in tetrahydrofuran/methanol (1:3, v/v) (5ml) and stirred for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue was taken up in 1M sodium hydroxide in water/methanol (5ml) and stirred for 1 hour. The solvent was removed *in vacuo* and the residu was partitioned between ethyl acetate and water and the layers separated. The aqueous layer was acidified to pH 3-4 with 5% citric acid solution, extracted with ethyl acetate and the organic layer washed with brine. The organic layer was then dried over magnesium sulfate, filtered and the filtrate concentrated *in vacuo* to give 2-(4-isobutrylamino-1H-pyrazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (140mg) as a white solid.

LC-MS (METHOD C): $R_T = 2.87$ minutes, 313.33 (M+H)⁺.

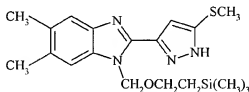
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EXAMPLE 2652-(1H-Indazol-3-yl)-3H-benzimidazol-5-amine

- 5 A stirred solution of 3-(5-nitro-1H-benzimidazol-2-yl)-1H-indazole [90.8 mg, Reference Example 233(as)] in methanol (1ml) was treated with tin chloride (616mg). The reaction was heated at reflux for 16 hours and then cooled to ambient temperature. The pH of the reaction mixture was adjusted to pH 8 by addition of aqueous sodium bicarbonate and then this mixture was extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and then evaporated to yield an oil. The crude
- 10 product was subjected to flash column chromatography on silica eluting with ethyl acetate and 10% triethylamine to give 2-(1H-indazol-3-yl)-3H-benzimidazol-5-amine (826mg). MS: 250.31 (M+H)⁺, 248.31 (M-H)⁻. HPLC (Method B): R_T – 2.03 minutes.

REFERENCE EXAMPLE 1

- 15 (a) 5,6-Dimethyl-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole



- A mixture of 1-[5,6-dimethyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-methylsulfonyl-propenone [318mg, Reference Example 2(a)], hydrazine (2mL) and ethanol (12mL)
- 20 was heated at reflux temperature for 1 hour. The reaction mixture was then cooled to room temperature, then stirred at room temperature overnight, then heated at 60°C for 2 hours, then heated at reflux temperature for 3 hours, then stood at room temperature for 3 days and then evaporated. The residue was dissolved in dichloromethane and this solution was washed with water plus a little brine to facilitate separation and the aqueous phase was washed with dichloromethane and then with ethyl
- 25 acetate. The combined organics were dried over magnesium sulfate and then evaporated to give 5,6-dimethyl-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole (90mg) as a colourless solid.

(b) By proceeding in a similar manner to Reference Example 1(a) above but using 1-[6-chloro-5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-methylsulfonyl-propenone [Reference Example 2(b)] there was prepared 6-chloro-5-methyl-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole.

5

(c) By proceeding in a similar manner to Reference Example 1(a) above but using 1-[6-chloro-5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-ethylsulfonyl-propenone [Reference Example 2(c)] there was prepared 6-chloro-5-methyl-2-(5-ethylsulfonyl-1H-pyrazol-3-yl)-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole

10

(d) By proceeding in a similar manner to Reference Example 1(a) above but using 3,3-bis-methylsulfonyl-1-[5-trifluoromethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-propenone [Reference Example 2(d)] there was prepared 2-(5-methylsulfonyl-1H-pyrazol-3-yl)-5-trifluoromethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole

15

(e) By proceeding in a similar manner to Reference Example 1(a) above but using 3,3-bis-cyclopropylmethylsulfonyl-1-[5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-propenone [Reference Example 2(e)] there was prepared 2-(5-cyclopropylmethylsulfonyl-1H-pyrazol-3-yl)-5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole.

20

(f) By proceeding in a similar manner to Reference Example 1(a) above but using 1-[5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-ethylsulfonyl propenone [Reference Example 2(f)] there was prepared 5,6-dimethyl-2-(5-ethylsulfonyl-1H-pyrazol-3-yl)-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole.

25

(g) By proceeding in a similar manner to Reference Example 1(a) above but using 1-[5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-(pyridin-3-ylmethylsulfonyl)-propenone [Reference Example 2(g)] there was prepared 5,6-dimethyl-2-(5-(pyridin-3-yl)methylsulfonyl-1H-pyrazol-3-yl)-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole.

30

(h) By proceeding in a similar manner to Reference Example 1(a) above but using 1-[5-fluoro-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-methylsulfonyl-propenone [Reference Example 2(h)] there was prepared 5-fluoro-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole.

35

(i) By proceeding in a similar manner to Reference Example 1(a) above but using 1-[5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-phenethylsulfanyl-propenone [Reference Example 2(i)] there was prepared 5,6-dimethyl-2-(5-phenethylsulfanyl-1H-pyrazol-3-yl)-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole.

5

(j) By proceeding in a similar manner to Reference Example 1(a) above but using 3,3-bis-methylsulfanyl-1-[4-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-propenone [Reference Example 2(k)] there was prepared 4-methyl-2-(5-methylsulfanyl-1H-pyrazol-3-yl)-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole.

10

(k) By proceeding in a similar manner to Reference Example 1(a) above but using 3,3-bis-benzylsulfanyl-1-[5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-propenone [Reference Example 2(o)] there was prepared 2-(5-benzylsulfanyl-1H-pyrazol-3-yl)-5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole.

15

(l) By proceeding in a similar manner to Reference Example 1(a) above but using 1-[6-chloro-5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3-methylsulfanyl-3-morpholin-1-yl-propenone [Reference Example 13] there was prepared 6-chloro-5-methyl-2-(5-morpholin-4-yl-1H-pyrazol-3-yl)-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole.

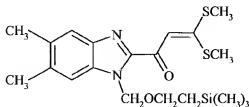
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(m) By proceeding in a similar manner to Reference Example 1(a) above but using 1-[5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-(thiophen-2-ylmethylsulfanyl)-propenone [Reference Example 2(s)] there was prepared 5,6-dimethyl-2-[5-(thiophen-2-ylmethylsulfanyl)-1H-pyrazol-3-yl]-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole.

25

REFERENCE EXAMPLE 2

(a) 1-[5,6-Dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-methylsulfanyl-propenone



30 A stirred suspension of sodium *tert*-butoxide (350mg) in benzene (6mL), at -5°C, was treated with a solution of 1-[5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone [240mg, Reference Example 3(a)] in benzene (5mL) followed by carbon disulfide (230μL). The

resulting orange solution was stirred for 1 hour at -5°C, then treated with methyl iodide (180µL), then allowed to warm to room temperature and then stirred at room temperature overnight. An orange precipitate was formed. The reaction mixture was poured into ice-water and this mixture was then extracted with dichloromethane. The combined organic extracts were washed with water, then dried
5 over sodium sulfate and then evaporated to give 1-[5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-methylsulfonyl-propenone (318mg) as an orange oil which was used without further purification.

(b) By proceeding in a similar manner to Reference Example 2(a) above but using 1-[6-chloro-5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone [Reference Example 3(b)] there was prepared 1-[6-chloro-5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-methylsulfonyl-propenone.

(c) By proceeding in a similar manner to Reference Example 2(a) above but using 1-[6-chloro-5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone [Reference Example 3(b)] and ethyl iodide there was prepared 1-[6-chloro-5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-ethylsulfonyl-propenone.

(d) By proceeding in a similar manner to Reference Example 2(a) above but using 1-[5-trifluoromethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone [Reference Example 3(c)] there was prepared 3,3-bis-methylsulfonyl-1-[5-trifluoromethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-propenone.

(e) By proceeding in a similar manner to Reference Example 2(a) above but using bromomethylcyclopropane there was prepared 3,3-bis-cyclopropylmethylsulfonyl-1-[5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-propenone.

(f) By proceeding in a similar manner to Reference Example 2(a) above but using ethyl iodide there was prepared 1-[5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-ethylsulfonyl-propenone.

(g) By proceeding in a similar manner to Reference Example 2(a) above but using 3-picolyl chloride there was prepared 1-[5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-(pyridin-3-ylmethylsulfonyl)-propenone.

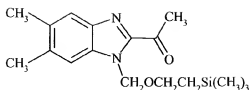
- (h) By proceeding in a similar manner to Reference Example 2(a) above but using 1-[5-fluoro-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone [Reference Example 3(d)] there was prepared 1-[5-fluoro-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-methylsulfonyl-propenone.
- 5 (i) By proceeding in a similar manner to Reference Example 2(a) above but using phenethyl bromide there was prepared 1-[5,6-dimethyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-3,3-bis-phenethylsulfonyl-propenone.
- 10 (j) By proceeding in a similar manner to Reference Example 2(a) above but using 1-[5-methoxy-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone [Reference Example 4(g)] and ethyl bromide there was prepared 3,3-bis-ethylsulfonyl-1-[5-methoxy-2-(trimethylsilyl)ethoxymethyl]-1H-benzimidazol-2-yl]-propenone.
- 15 (k) By proceeding in a similar manner to Reference Example 2(a) above but using 1-[4-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone [Reference Example 3(e)] there was prepared 3,3-bis-methylsulfonyl-1-[4-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-propenone.
- 20 (l) By proceeding in a similar manner to Reference Example 2(a) above but using 1-[5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-pentan-1-one [Reference Example 3(f)] there was prepared 2-(bis-methylsulfonyl-methylene)-1-(5-methyl-1H-benzimidazol-2-yl)-pentan-1-one.
- 25 (m) By proceeding in a similar manner to Reference Example 2(a) above but using 1-[5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-pentan-1-one [Reference Example 3(f)] and 4-methoxybenzyl chloride there was prepared 2-[bis-(4-methoxy-benzylsulfonyl)-methylene]-1-(5-methyl-1H-benzimidazol-2-yl)-pentan-1-one.
- 30 (n) By proceeding in a similar manner to Reference Example 2(a) above but using 3-methyl-1-[5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-butan-1-one [Reference Example 3(g)] and benzyl chloride there was prepared 2-(bis-benzylsulfonyl-methylene)-3-methyl-1-[5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-butan-1-one.

- (o) By proceeding in a similar manner to Reference Example 2(a) above but using benzyl chloride there was prepared 3,3-bis-benzylsulfanyl-1-[5,6-dimethyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-propanone.
- 5 (p) By proceeding in a similar manner to Reference Example 2(a) above but using 1-[1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-ethanone [Reference Example 4(h)] with tetrahydrofuran as the solvent and carrying out the reaction at room temperature and then subjecting the reaction product to flash chromatography on silica under gradient elution conditions (20 to 33% ethyl acetate in pentane) there was prepared 3,3-bis-methanesulfanyl-1-[1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-propanone as an oil which slowly solidified on standing at room temperature.
- 10 (q) By proceeding in a similar manner to Reference Example 2(a) above but using 1-[6-chloro-5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-ethanone [Reference Example 3(b)] and methyl iodide there was prepared 1-[6-chloro-5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-3,3-bis-methylsulfanyl-propanone.
- 15 (r) By proceeding in a similar manner to Reference Example 2(a) above but using 1-[5-methoxy-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-propan-1-one [Reference Example 4(i)] and methyl iodide there was prepared 1-[5-methoxy-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-2-methyl-3-(bis-methanesulfanyl)-1-propanone.
- 20 (s) By proceeding in a similar manner to Reference Example 2(a) above but using of 1-[5,6-dimethyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-ethanone [Reference Example 3(a)] and 2-chloromethylthiophene [Reference Example 14]) there was prepared 1-[5,6-dimethyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-3,3-bis-(thiophen-2-yl)methylsulfanyl)-propanone.
- 25 (t) By proceeding in a similar manner to Reference Example 2(a) above but using 1-[5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-propan-1-one [Reference Example 3(h)] there was prepared 1-[5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-2-methyl-3-(bis-methanesulfanyl)-1-propanone.
- 30

REFERENCE EXAMPLE 3

- 35 (a) 1-[5,6-Dimethyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzoimidazol-2-yl]-ethanone

-472-

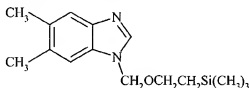


- A solution of 5,6-dimethyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole [5.01g, Reference Example 4(a)] in dry tetrahydrofuran (55mL), at -78°C, was treated with a solution of lithium diisopropylamide in a mixture of tetrahydrofuran and heptane (11.9mL, 2M) over 10 minutes. The mixture was stirred for 15 minutes then treated dropwise with dimethylacetamide (2.15mL) over 10 minutes. After stirring at -78°C for a further 30 minutes the reaction mixture was poured into ice (50g) and then left until all the ice had melted. This mixture was extracted with dichloromethane and the extracts were washed with brine, then with water, then dried over magnesium sulfate and then evaporated. The residual orange oil (5.91g) was subjected to column chromatography on silica eluting with a mixture of petroleum ether and ethyl acetate (4:1, v/v) to give 1-[5,6-dimethyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone (3.93g) as a yellow crystalline solid.
- (b) By proceeding in a similar manner to Reference Example 3(a) above but using 6-chloro-5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole [Reference Example 4(b)] there was prepared 1-[6-chloro-5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone.
- (c) By proceeding in a similar manner to Reference Example 3(a) above but using 5-trifluoromethyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole [Reference Example 4(c)] there was prepared 1-[5-trifluoromethyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone.
- (d) By proceeding in a similar manner to Reference Example 3(a) above but using 5-fluoro-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole [Reference Example 4(d)] there was prepared 1-[5-fluoro-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone.
- (e) By proceeding in a similar manner to Reference Example 3(a) above but using 4-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole [Reference Example 4(e)] there was prepared 1-[4-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone.
- (f) By proceeding in a similar manner to Reference Example 3(a) above but using 5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole [Reference Example 4(f)] and dimethylvaleramide [Reference Example 8(a)] there was prepared 1-[5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-pentan-1-one.

- (g) By proceeding in a similar manner to Reference Example 3(a) above but using 5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole [Reference Example 4(f)] and dimethylisovalerylamide [Reference Example 8(b)] there was prepared 3-methyl-1-[5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-butan-1-one.
- (h) By proceeding in a similar manner to Reference Example 3(a) above but using 5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole [Reference Example 4(f)] and dimethylpropionamide there was prepared 1-[5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-propan-1-one.

REFERENCE EXAMPLE 4

- (a) 5,6-Dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole

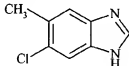


- 15 A stirred mixture of sodium hydride (1.08g) in dimethylformamide (80mL) was treated with a solution of 5,6-dimethyl-1H-benzimidazole (4.95g) in dimethylformamide (50mL) at room temperature over 10 minutes. After stirring for a further 1 hour the mixture was then treated with 2-(trimethylsilyl)ethoxymethyl chloride (6.4mL) over 15 minutes and then stirring was continued for 18 hours. The reaction mixture was treated with methanol (15mL) and water (1mL) and then
- 20 evaporated. The residue was treated with water (50mL) and this mixture was then extracted twice with diethyl ether (80mL then 50mL). The combined extracts were washed three times with water (50mL), then dried over magnesium sulfate and then evaporated. The residual brown oil (10.3g) was purified by Flashmaster using mixtures of ethyl acetate in hexane (20% to 80%) at 40mL/minute to give 5,6-dimethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole (7.54g) as an orange oil.
- 25
- (b) By proceeding in a similar manner to Reference Example 4(a) above but using 6-chloro-5-methyl-1H-benzimidazole [Reference Example 5(a)] there was prepared 6-chloro-5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole.
- 30 (c) By proceeding in a similar manner to Reference Example 4(a) above but using 5-trifluoromethyl-1H-benzimidazole [Reference Example 5(b)] there was prepared 5-trifluoromethyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole.

- (d) By proceeding in a similar manner to Reference Example 4(a) above but using 5-fluoro-1H-benzimidazole [Reference Example 5(c)] there was prepared 5-fluoro-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole.
- 5 (e) By proceeding in a similar manner to Reference Example 4(a) above but using 4-methyl-1H-benzimidazole [Reference Example 5(d)] there was prepared 4-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole.
- (f) By proceeding in a similar manner to Reference Example 4(a) above but using 5-methyl-1H-
- 10 benzimidazole there was prepared 5-methyl-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole.
- (g) By proceeding in a similar manner to Reference Example 4(a) above but using 1-(5-methoxy-1H-benzimidazol-2-yl)-ethanone [Reference Example 6(a)] there was prepared 1-[5-methoxy-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone.
- 15
- (h) By proceeding in a similar manner to Reference Example 4(a) above but using (1H-benzimidazol-2-yl)-1-ethanone and carrying out the reaction in tetrahydrofuran there was prepared 1-[1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-ethanone as a colourless oil.
- 20 (i) By proceeding in a similar manner to Reference Example 4(a) above but using 1-(5-methoxy-1H-benzimidazol-2-yl)-propan-1-one [Reference Example 6(b)] there was prepared 1-[5-methoxy-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-propan-1-one

REFERENCE EXAMPLE 5

- 25 (a) 6-chloro-5-methyl-1H-benzimidazole



- A solution of 5-chloro-4-methyl-1,2-phenylenediamine (7.8g) in a mixture of formic acid (35mL) and hydrochloric acid (300mL) was heated at 50°C for 3 hours then treated with ammonium hydroxide solution until the solution was basic. The reaction mixture was then extracted with dichloromethane.
- 30 The extracts were evaporated to give 6-chloro-5-methyl-1H-benzimidazole (7g).

- (b) By proceeding in a similar manner to Reference Example 5(a) above but using 4-trifluoromethyl-1,2-phenylenediamine there was prepared 5-trifluoromethyl-1H-benzimidazole.

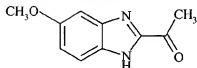
(c) By proceeding in a similar manner to Reference Example 5(a) above but using 4-fluoro-*o*-phenylenediamine there was prepared 5-fluoro-1H-benzimidazole.

(d) By proceeding in a similar manner to Reference Example 5(a) above but using

- 5 2,3-diaminotoluene there was prepared 4-methyl-1H-benzimidazole.

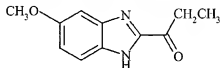
REFERENCE EXAMPLE 6

- (a) 1-(5-Methoxy-1H-benzimidazol-2-yl)-ethanone



- 10 A stirred mixture of 1-(5-methoxy-1H-benzimidazol-2-yl)-ethanol [5.14g, Reference Example 7(a)] and manganese dioxide (9g) in chloroform (80mL) was heated at 60°C for 18 hours, then cooled to room temperature and then filtered. The filtrate was evaporated to give 1-(5-methoxy-1H-benzimidazol-2-yl)-ethanone (4.28g).

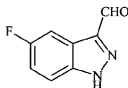
- 15 (b) 1-(5-Methoxy-1H-benzimidazol-2-yl)-propan-1-one



By proceeding in a similar manner to Reference Example 6(a) above but using 1-(5-methoxy-1H-benzimidazol-2-yl)-propanol [Reference Example 7(b)] there was prepared 1-(5-methoxy-1H-benzimidazol-2-yl)-propan-1-one.

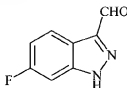
20

- (c) 5-Fluoro-1H-indazole-3-carbaldehyde

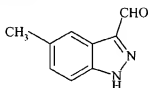


By proceeding in a similar manner to Reference Example 6(a) above but using (5-fluoro-1H-indazol-3-yl)-methanol [Reference Example 25(a)] with acetone as the solvent, a reaction temperature of 55°C

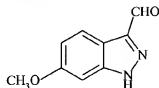
- 25 and subjecting the reaction product to flash column chromatography on silica eluting with a mixture of 40/60 petrol and ethyl acetate (1:1 v/v) there was prepared 5-fluoro-1H-indazole-3-carbaldehyde as a light brown solid. LC-MS (METHOD B): R_T = 2.74 minutes, 165 (M+H)⁺.

(d) 6-Fluoro-1H-indazole-3-carbaldehyde

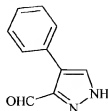
- By proceeding in a manner similar to Reference Example 6(a) above but using (6-fluoro-1H-indazol-3-yl)-methanol [Reference Example 25(b)] with acetone as the solvent, a reaction temperature of 55°C and subjecting the reaction product to flash column chromatography on silica eluting with a mixture of 40/60 petrol and ethyl acetate (1:1 v/v) there was prepared 6-fluoro-1H-indazole-3-carbaldehyde as a light brown solid. LC-MS (METHOD B): $R_T = 2.74$ minutes, 165 (M+H)⁺.

(e) 5-Methyl-1H-indazole-3-carbaldehyde

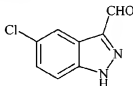
- By proceeding in a manner similar to Reference Example 6(a) above but using (5-methyl-1H-indazol-3-yl)-methanol [Reference Example 25(c)] with dichloromethane as solvent, a reaction temperature of 40°C and subjecting the reaction product to flash column chromatography on silica eluting with a mixture of hexane and ethyl acetate (1:1, v/v) there was prepared 5-methyl-1H-indazole-3-carbaldehyde as a pale brown solid. LC-MS (METHOD B): $R_T = 2.79$ minutes, 161 (M+H)⁺.

(f) 6-Methoxy-1H-indazole-3-carbaldehyde

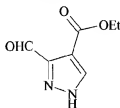
- By proceeding in a manner similar to Reference Example 6(a) above but using (6-methoxy-1H-indazol-3-yl)-methanol [Reference Example 25(e)] with acetone as the solvent, a reaction temperature of 55°C and subjecting the reaction product to flash column chromatography on silica eluting with a mixture of 40/60 petrol and ethyl acetate (1:1 v/v) there was prepared 6-methoxy-1H-indazole-3-carbaldehyde as a light brown solid. LC-MS (METHOD B): $R_T = 2.76$ minutes, 177 (M+H)⁺.

(g) 4-Phenyl-1H-pyrazole-3-carbaldehyde

By proceeding in a similar manner to Reference Example 6(a) above but using (4-phenyl-1H-pyrazol-3-yl)-methanol [Reference Example 25(f)] with acetone as the solvent, a reaction temperature of 60°C for 2 hours, and subjecting the reaction product to flash column chromatography on silica eluting with a mixture of dichloromethane and methanol (49:1, v/v) there was prepared 4-phenyl-1H-pyrazole-3-carbaldehyde as a white solid. LC-MS (METHOD B): $R_T = 2.76$ minutes; 213 (M+H)⁺.

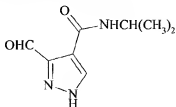
(h) 5-Chloro-1H-indazole-3-carbaldehyde

By proceeding in a similar manner to Reference Example 6(a) above but using (5-chloro-1H-indazol-3-yl)-methanol [Reference Example 25(d)] with a mixture of dichloromethane and tetrahydrofuran as solvent, heating at reflux temperature and subjecting the reaction product to flash column chromatography on silica eluting with a mixture of hexane and ethyl acetate (1:1, v/v) there was prepared 5-chloro-1H-indazole-3-carbaldehyde as a pale brown solid. LC-MS (METHOD B): $R_T = 2.89$ minutes, 181 (M+H)⁺.

(i) 3-Formyl-pyrazole-4-carboxylic acid ethyl ester

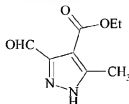
By proceeding in a manner similar to Reference Example 6(a) above but using 3-hydroxymethyl-1H-pyrazole-4-carboxylic acid ethyl ester [Reference Example 41(a)] there was prepared 3-formyl-pyrazole-4-carboxylic acid ethyl ester as a brown solid. LC-MS (METHOD B): $R_T = 2.65$ minutes; 169 (M+H)⁺.

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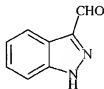
(j) 3-Formyl-pyrazole-4-carboxylic acid isopropylamide

By proceeding in a manner similar to Reference Example 6(a) above but using 3-hydroxymethyl-1H-pyrazole-4-carboxylic acid isopropylamide [Reference Example 41(b)] there was prepared 3-formyl-pyrazole-4-carboxylic acid isopropylamide as a waxy orange solid. LC-MS (METHOD B): $R_T = 2.73$

- 5 minutes; 182 (M+H)⁺.

(k) 3-Formyl-5-methyl-pyrazole-4-carboxylic acid ethyl ester

- 10 By proceeding in a manner similar to Reference Example 6(a) above but using 3-hydroxymethyl-5-methyl-1H-pyrazole-4-carboxylic acid ethyl ester [Reference Example 41(c)] there was prepared 3-formyl-5-methyl-pyrazole-4-carboxylic acid ethyl ester as a white solid. LC-MS (METHOD B): $R_T = 2.80$ minutes; 183 (M+H)⁺.

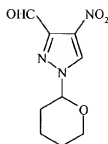
15 (l) 1H-indazole-3-carbaldehyde

By proceeding in a manner similar to Reference Example 6(a) above but using (1H-indazol-3-yl)-methanol [Reference Example 25(g)] with acetone as the solvent and carrying out the reaction at reflux temperature for 16 hours there was prepared 1H-indazole-3-carbaldehyde as a yellow solid.

- 20 LC-MS [METHOD B]; $R_T = 2.63$ minutes; 147.26 (M+H)⁺; 145.26 (M-H)⁻.

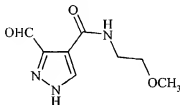
(m) 4-Nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carbaldehyde

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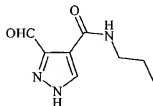
- By proceeding in a manner similar to Reference Example 6(a) above but (i) using [4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-methanol (663mg, Reference Example 53) and manganese (IV) oxide (2.54g) with acetone as the solvent, (ii) carrying out the reaction at 65°C for 2 hours and
- 5 (iii) subjecting the reaction product to flash silica chromatography eluting with a mixture of pentane and ethyl acetate (70:30, v/v), there was prepared 4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carbaldehyde (191mg) as a pale yellow oil. LC-MS (Method H): $R_T = 2.19$ minutes, 248.24 (M+H+Na)⁺.

- 10 (n) 3-Formyl-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide

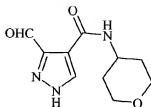


- By proceeding in a manner similar to Reference Example 6(a) above but using 3-hydroxymethyl-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide [Reference Example 41(d)] there was prepared 3-formyl-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide (325mg) as a yellow oil. LC-MS
- 15 (METHOD B): $R_T = 2.13$ minutes, 198 (M+H)⁺.

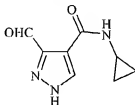
- (o) 3-Formyl-1H-pyrazole-4-carboxylic acid propylamide



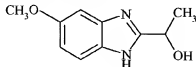
- By proceeding in a manner similar to Reference Example 6(a) above but using 3-hydroxymethyl-1H-pyrazole-4-carboxylic acid propylamide [Reference Example 41(e)] there was prepared 3-formyl-1H-pyrazole-4-carboxylic acid propylamide (414mg) as an orange oil. LC-MS (METHOD B): $R_T = 2.42$ minutes, 182 (M+H)⁺.
- 20

(p) 3-Formyl-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide

By proceeding in a manner similar to Reference Example 6(a) above but using 3-hydroxymethyl-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide [Reference Example 41(f)] there was prepared 3-formyl-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide (400mg) as a brown oil. LC-MS (METHOD N): $R_T = 2.34$ minutes, 224.31 (M+H)⁺.

(q) 3-Formyl-1H-pyrazole-4-carboxylic acid cyclopropylamide

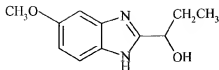
By proceeding in a manner similar to Reference Example 6(a) above but using 3-hydroxymethyl-1H-pyrazole-4-carboxylic acid cyclopropylamide [Reference Example 41(f)] there was prepared 3-formyl-1H-pyrazole-4-carboxylic acid cyclopropylamide (125mg) as a yellow oil. LC-MS (METHOD H): $R_T = 1.87$ minutes, 178.31 (M-H)⁻.

REFERENCE EXAMPLE 7(a) 1-(5-Methoxy-1H-benzimidazol-2-yl)-ethanol

A mixture of 4-methoxy-phenylenediamine dihydrochloride (10g), sodium L-lactate (10g) and hydrochloric acid (60mL, 4M) was heated at 70°C for 48 hours. The reaction mixture was cooled to room temperature, then treated with ammonium hydroxide. The resulting precipitate was filtered and dried to give 1-(5-methoxy-1H-benzimidazol-2-yl)-ethanol (5.14g).

(b) 1-(5-Methoxy-1-benzimidazole)-1-propanol

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By proceeding in a similar manner to Reference Example 7(a) above but using 2-hydroxybutyric acid there was prepared 1-(5-methoxy-1-benzimidazole)-1-propanol.

5

REFERENCE EXAMPLE 8(a) Dimethylvaleramide

A solution of dimethylamine hydrochloride (6.76g) and triethylamine (30mL) in dichloromethane (100mL), under nitrogen and at 0°C was treated dropwise with valeryl chloride (10g). After stirring at room temperature overnight the reaction mixture was treated with hydrochloric acid (2N) and dichloromethane. The organic phase was separated, dried over magnesium sulfate and then evaporated to give dimethylvaleramide as a clear oil.

10

(b) By proceeding in a similar manner to Reference Example 8(a) above but using isovaleryl chloride there was prepared dimethylisovalerylamide.

15

REFERENCE EXAMPLE 92,3-Diaminopyrazine

Liquid ammonia (50mL) was introduced into a pressure reaction vessel containing a small lump of ice. To this was added copper bronze (1.17g), copper (II) iodide (0.224g) and 2,3-dichloropyrazine (4g). The sealed reaction vessel was heated at 170°C for 48 hours, then cooled to ambient temperature and then vented. The reaction mixture was treated with water (75mL) and this mixture was extracted four times with diethyl ether (400mL). The combined extracts were evaporated to give 2,3-diaminopyrazine as a white solid (0.3g). The aqueous layer was continuously extracted with diethyl ether for 18 hours to yield a further quantity of 2,3-diaminopyrazine (1.24g). ¹H-NMR [(CD₃)₂SO]: δ 5.87 (s, 4H), 7.15 (s, 2H).

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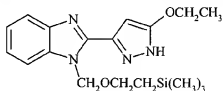
REFERENCE EXAMPLE 101H-Pyrazole-3-carbaldehyde

(i) Dry dimethylformamide (77.6mL) was stirred at 80°C while cyanuric chloride (26.6g) was added in portions, whilst keeping the reaction temperature between 80 and 110°C. The reaction mixture was stirred at 100°C for another 30 minutes then cooled and then allowed to stand at room temperature overnight. The reaction mixture was filtered to give dimethylvinylamine.

30

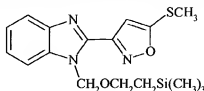
- (ii) The dimethylvinylamine from (i) was added to dry methanol (260mL) and the mixture was then treated with pyruvic aldehyde dimethylacetal (51mL), followed by a solution of sodium methoxide in methanol (30%, 81mL), then stirred for 2 hours at ambient temperature, then heated at reflux temperature for another hour, then cooled and then filtered. The filtrate was evaporated to give
- 5 1,1-dimethoxy-but-3-en-2-one as a brown oil (96.8g).
- (iii) A stirred solution of 1,1-dimethoxy-but-3-en-2-one in water (300mL) was treated dropwise with hydrazine hydrate (21 mL). After standing at room temperature overnight the reaction mixture was treated with sodium chloride (108g) and the mixture was then extracted with methyl-t-butyl ether (200mL then 100mL). The combined extracts were dried with magnesium sulfate and then evaporated
- 10 to give 1H-pyrazol-3-carbaldehyde dimethyl acetal as a light brown oil (18.47g).
- (iv) A solution of 1H-pyrazol-3-carbaldehyde dimethyl acetal in water (85mL) was treated with glacial acetic acid (3.7mL). After two days the mixture was filtered to give 1H-pyrazole-3-carbaldehyde (1.3g) as a light brown solid.

15

REFERENCE EXAMPLE 112-(5-Ethoxy-1H-pyrazol-3-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole

- Sodium hydride (0.1g) was added to ethanol (5mL) and the mixture was stirred for ten minutes, then treated with 3,3-bis- methanesulfanyl-1-[1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazol-2-yl]-
- 20 propenone [0.5g, Reference Example 2(p)] and then heated at reflux temperature for six hours. The reaction mixture was cooled, then treated with hydrazine hydrate (1.27mmol) and then heated at reflux temperature for four hours. The mixture was then evaporated and the residue was triturated with water and filtered. The solid was subjected to chromatography on silica gel eluting with ethyl acetate to give
- 2-(5-ethoxy-1H-pyrazol-3-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole as a yellow oil.

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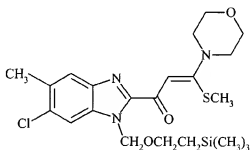
REFERENCE EXAMPLE 122-(5-Methylsulfanyl-isoxazol-3-yl)-1-(2-trimethylsilyl-ethoxymethyl)-1H-benzimidazole

- Hydroxylamine hydrochloride (168mg) was added to a solution of sodium methoxide in methanol
- 30 [prepared by the addition of sodium hydride (122mg) to methanol (5mL)]. The mixture was stirred for

- ten minutes, then treated with 3,3-bis-methanesulfanyl-1-[1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]-propenone [500mg, Reference Example 2(p)], then heated at reflux for six hours, then cooled and then evaporated. The residue was taken up in water and the aqueous mixture was extracted with ethyl acetate. The extracts were dried and evaporated. The residue was subjected to
- 5 chromatography on silica eluting with methylene chloride to give 2-(5-methylsulfanyl-isoxazol-3-yl)-1-(trimethylsilylanyl-ethoxymethyl)-1H-benzimidazole (0.16 g) as a colourless oil.

REFERENCE EXAMPLE 13

- 1-[6-Chloro-5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]- 3-methylsulfanyl-3-morpholin-1-yl-propenone
- 10



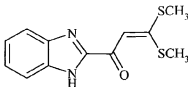
- A solution of 1-[6-chloro-5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]- 3,3-bis-methanesulfanyl-propenone [800mg, Reference Example 2(q)] in morpholine (3mL) was heated at 95°C for 2 hours and then evaporated to give 1-[6-chloro-5-methyl-1-(2-trimethylsilylanyl-ethoxymethyl)-1H-benzimidazol-2-yl]- 3-methylsulfanyl-3-morpholin-1-yl-propenone.
- 15

REFERENCE EXAMPLE 14

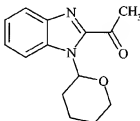
2-Chloromethyl-thiophene



- To a three-necked flask fitted with stirrer bar, pressure equalizing dropping funnel and inlet/outlet adapter was added thiophene (10mL) and aqueous hydrochloric acid (5.5mL). Hydrogen chloride gas [generated by dropping sulfuric acid (30mL) onto dry sodium chloride (50 g)] was bubbled through the reaction mixture with vigorous stirring at 0°C. This mixture was then treated dropwise with formaldehyde solution (37%, 12.5mL) and stirring was continued for 45 minutes. The phases were
- 25 separated and the aqueous phase was extracted three times with diethyl ether (10mL). The organic phases were then washed twice with water (10mL), then twice with saturated sodium hydrogen carbonate (10mL), then dried over magnesium sulfate and then evaporated. The residue was distilled at 20 mmHg using a heat gun to give 2-chloromethyl-thiophene which was used immediately without further purification.

REFERENCE EXAMPLE 15Bis(methylthio)-3,3-(benzimidazol-2-yl)-1-prop-2-en-2-one

- 5 A mixture of sodium hydride (19.2g) and toluene (400mL), at 80°C, was treated portionwise with tertiary-butanol (30.8g). After 2 hours the reaction mixture was cooled to room temperature and treated dropwise with a mixture of dimethylformamide (40mL), carbon disulfide (12mL) and 2-acetyl-1-(tetrahydropyran-2-yl)-benzimidazole (51g, Reference Example 16) over 90 minutes. After addition the red reaction mixture was stirred at 80°C for 30 minutes, then cooled to room temperature and then
- 10 treated with methyl iodide (50mL). This mixture was stirred at 80°C for 30 minutes when a precipitate started to form. The reaction mixture was cooled to room temperature and then filtered. The filtrate was concentrated to give a viscous red oil, which was dissolved in methanol (300mL). This solution was treated with p-toluenesulfonic acid (2g) and water (4mL), then heated at reflux temperature for 13 hours and then cooled in an ice-bath. The resulting solid was filtered and then washed with isopropyl
- 15 ether to give bis(methylthio)-3,3-(benzimidazol-2-yl)-1-prop-2-en-2-one (11.2g), m.p. 224°C.

REFERENCE EXAMPLE 162-Acetyl-1-(tetrahydropyran-2-yl)-benzimidazole

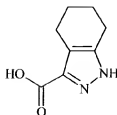
- 20 Dihydropyran (20.5mL) as added dropwise to a solution of 2-acetylbenzimidazole (32g) and p-toluenesulfonic acid (2g) in dichloromethane (280mL) at reflux. The reaction mixture was stirred at this temperature for 24 hours, then cooled and the insoluble materials were filtered off. The filtrate was concentrated to give 2-acetyl-1-(tetrahydropyran-2-yl)-benzimidazole as an amber oil (51.8g). TLC: (dichloromethane:methanol, 97:3) R_f = 0.80.

25

REFERENCE EXAMPLE 17

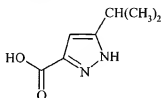
- (a) 4,5,6,7-Tetrahydro-1H-indazole-3-carboxylic acid

-485-



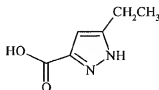
- A solution of 4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid ethyl ester [0.606g, Reference Example 18(a)] in methanol (50ml) was treated with sodium hydroxide (0.500g). The mixture was refluxed for 16 hours, then cooled and then evaporated. The residual white solid was treated with hydrochloric acid (30ml, 2N) and the resulting solution was extracted three times with ethyl acetate (50ml). The combined organic extracts were dried over sodium sulfate and then evaporated to yield 4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (0.424g) as a white solid. LC-MS (METHOD B): $R_T=2.44$ minutes; 167 (M+H)⁺.

- 10 (b) 5-Isopropyl-1H-pyrazole-3-carboxylic acid



- By proceeding to a manner similar to Example 17(a) above but using 5-isopropyl-1H-pyrazole-3-carboxylic acid ethyl ester [Reference Example 18(b)], there was prepared 5-isopropyl-1H-pyrazole-3-carboxylic acid as a white solid (0.973g) which was used without further purification.
- 15 LC-MS (METHOD B): $R_T=2.43$ minutes; 155 (M+H)⁺.

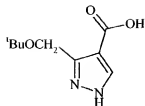
- (c) 5-Ethyl-1H-pyrazole-3-carboxylic acid



- By proceeding in a manner similar to Reference Example 17(a) above, but using 5-ethyl-1H-pyrazole-3-carboxylic acid ethyl ester [Reference Example 18(c)], there was prepared 5-ethyl-1H-pyrazole-3-carboxylic acid as a white solid. LC-MS (METHOD B): $R_T=2.34$ minutes; 141 (M+H)⁺.

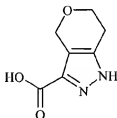
- (d) 3-tert-Butyloxymethyl-1H-pyrazole-4-carboxylic acid

-486-



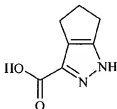
- By proceeding in a manner similar to Reference Example 17(a) above, but using 3-*tert*-butyloxymethyl-1H-pyrazole-4-carboxylic acid ethyl ester [Reference Example 42], there was prepared 3-*tert*-butyloxymethyl-1H-pyrazole-4-carboxylic acid as a white solid which was used without further
- 5 purification. LC-MS (METHOD B): R_T = 2.75 minutes; 199 (M+H)⁺.

(e) 1,4,6,7-Tetrahydro-pyrano[4,3-c]pyrazole-3-carboxylic acid



- By proceeding in a manner similar to Reference Example 17(a) above but using 1,4,6,7-tetrahydro-pyrano[4,3-c]pyrazole-3-carboxylic acid ethyl ester [Reference Example 18(e)] there was prepared 1,4,6,7-tetrahydro-pyrano[4,3-c]pyrazole-3-carboxylic acid (261 mg) as a white solid. LC-MS
- 10 (METHOD B): R_T = 1.98 minutes, 169 (M+H)⁺.

(f) 1,4,5,6-Tetrahydro-cyclopentapyrazole-3-carboxylic acid



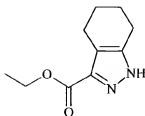
- By proceeding in a manner similar to Reference Example 17(a) above but using 1,4,5,6-tetrahydro-cyclopentapyrazole-3-carboxylic acid ethyl ester [Reference Example 18(f)] there was prepared 1,4,5,6-tetrahydro-cyclopentapyrazole-3-carboxylic acid (0.641 g) as a white solid. LC-MS (METHOD
- 15 B): R_T = 2.13 minutes, 153.22 (M+H)⁺.

20

REFERENCE EXAMPLE 18

- (a) 4,5,6,7-Tetrahydro-1H-indazole-3-carboxylic acid ethyl ester

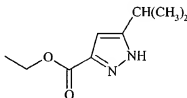
-487-



A solution of oxo-(2-oxo-cyclohexyl)-acetic acid ethyl ester [7.5g, Reference Example 19(a)] in acetic acid (150ml) was treated dropwise with hydrazine monohydrate (1.65ml). The mixture was refluxed for 8 hours, then cooled and then evaporated. The residue was partitioned between ethyl acetate (200ml) and saturated sodium bicarbonate solution (200ml) and the organic layer was dried over sodium sulfate and then evaporated. The residual orange oil was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and hexane (1:1, v/v) to give 4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid ethyl ester (606mg) as an orange oil which solidified on standing. LC-MS (METHOD B): R_T = 2.79 minutes; 195 (M+H)⁺.

10

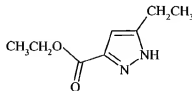
(b) 5-Isopropyl-1H-pyrazole-3-carboxylic acid ethyl ester



By proceeding to a manner similar to Reference Example 18(a) above but using 5-methyl-2,4-dioxo-hexanoic acid ethyl ester [2.00g, Reference Example 19(b)] there was prepared 5-isopropyl-1H-pyrazole-3-carboxylic acid ethyl ester as a light yellow oil which was used without further purification. LC-MS (METHOD B): R_T = 2.79 minutes; 183 (M+H)⁺.

15

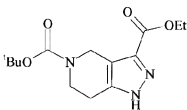
(c) 5-Ethyl-1H-pyrazole-3-carboxylic acid ethyl ester



By proceeding in a manner similar to Reference Example 18(a) above, but using 2,4-dioxo-hexanoic acid ethyl ester [Reference Example 19(c)], and subjecting the reaction product, an orange oil, to flash chromatography on silica eluting with a mixture of ethyl acetate and hexane (8:1, v/v), there was prepared 5-ethyl-1H-pyrazole-3-carboxylic acid ethyl ester as a yellow oil. LC-MS (METHOD B): R_T = 2.64 minutes; 169 (M+H)⁺.

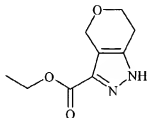
20

- (d) 1,4,6,7-Tetrahydro-pyrazolo[4,3-c]pyridine-3,5-dicarboxylic acid 5-*tert*-butyl ester 3-ethyl ester



- 5 By proceeding in a manner similar to Reference Example 18(a) above, but using 3-ethoxyoxalyl-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester [Reference Example 19(d)], there was prepared 1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-3,5-dicarboxylic acid 5-*tert*-butyl ester 3-ethyl ester as a yellow oil. LC-MS (METHOD B): $R_T = 2.73$ minutes; 296 (M+H)⁺.

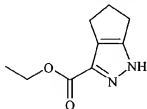
- 10 (e) 1,4,6,7-Tetrahydro-pyrano[4,3-c]pyrazole-3-carboxylic acid ethyl ester



By proceeding in a manner similar to Reference Example 18(a) above but using tetrahydro-4H-pyran-4-one there was prepared 1,4,6,7-tetrahydro-pyrano[4,3-c]pyrazole-3-carboxylic acid ethyl ester (385mg) as a white solid. LC-MS (METHOD B): $R_T = 2.43$ minutes, 197 (M+H)⁺.

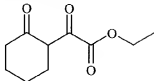
15

- (f) 1,4,5,6-Tetrahydro-cyclopentapyrazole-3-carboxylic acid ethyl ester



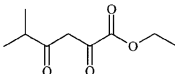
- 20 By proceeding in a manner similar to Reference Example 18(a) above but using oxo-(2-oxo-cyclopentyl)-acetic acid ethyl ester [Reference Example 19(e)] there was prepared 1,4,5,6-tetrahydro-cyclopentapyrazole-3-carboxylic acid ethyl ester (2.06g) as a yellow solid. LC-MS (METHOD B): $R_T = 2.56$ minutes, 185 (M+H)⁺.

REFERENCE EXAMPLE 19

(a) Oxo-(2-oxo-cyclohexyl)-acetic acid ethyl ester

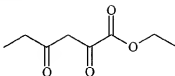
A solution of sodium (1.75g) in ethanol (100ml) was treated with a mixture of diethyl oxalate (9.41ml) and cyclohexanone (7.18ml). The mixture was heated to 60°C for 5 hours then cooled and then

- 5 evaporated to yield oxo-(2-oxo-cyclohexyl)-acetic acid ethyl ester as a brown foam (16.635g). LC-MS (METHOD B): $R_T = 3.10$ minutes; 197 (M-H)⁻.

(b) 5-Methyl-2,4-dioxo-hexanoic acid ethyl ester

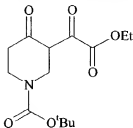
10

By proceeding to a manner similar to Example 19(a) above but using 3-methyl-2-butanone there was prepared 5-methyl-2,4-dioxo-hexanoic acid ethyl ester as a white solid. LC-MS (METHOD B): $R_T = 3.47$ minutes; 187 (M+H)⁺.

15 (c) 2,4-Dioxo-hexanoic acid ethyl ester

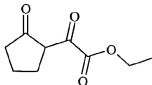
By proceeding in a manner similar to Reference Example 19(a) above, but using 2-butanone, there was prepared 2,4-dioxo-hexanoic acid ethyl ester as a brown oil which was used without further purification. LC-MS (METHOD B): $R_T = 3.28$ minutes; 173 (M+H)⁺.

20

(d) 3-Ethoxyoxalyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester

By proceeding in a manner similar to Reference Example 19(a) above, but using N-Boc piperidone, there was prepared 3-ethoxyoxalyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester as a brown oil which was used without further purification. LC-MS (METHOD B): $R_T=3.43$ minutes; 244 (M+Bu)⁺.

5 (e) Oxo-(2-oxo-cyclopentyl)-acetic acid ethyl ester

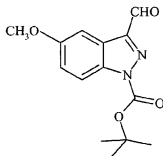


By proceeding in a manner similar to Reference Example 19(a) above but using cyclopentanone there was prepared oxo-(2-oxo-cyclopentyl)-acetic acid ethyl ester (9.99g) as a yellow solid. LC-MS (METHOD B): $R_T = 3.12$ minutes, 185 (M+H)⁺.

10

REFERENCE EXAMPLE 20

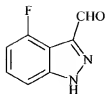
(a) 3-Formyl-5-methoxy-indazole-1-carboxylic acid tert-butyl ester



- 15 A solution of 5-methoxy-3-(2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester [282mg, Reference Example 21(a)] in tetrahydrofuran (4ml) and water (1.5ml) was treated with a solution of osmium tetroxide in water (54μL, 4wt%) and sodium periodate (400mg). The reaction mixture was stirred at ambient temperature for 16 hours and then filtered. The filtrate was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate and then evaporated. The residue was subjected to flash column chromatography
- 20 on silica eluting with a mixture of ethyl acetate and petrol (1:9, v/v) to yield 3-formyl-5-methoxy-indazole-1-carboxylic acid tert-butyl ester (162mg) as a white solid. LC-MS (METHOD B): $R_T = 2.97$ minutes; 277 (M+H)⁺.

(b) 4-Fluoro-1H-indazole-3-carbaldehyde

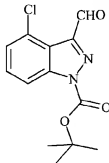
-491-



By proceeding in a manner similar to Reference Example 20(a) but using 4-fluoro-3-(2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester [Reference Example 21(b)] there was prepared 4-fluoro-1H-indazole-3-carbaldehyde as a light brown solid. LC-MS (METHOD B): R_T

5 \approx 2.63 minutes; 165 (M+H)⁺.

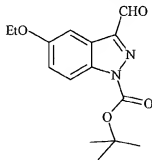
(c) 4-Chloro-3-formyl-indazole-1-carboxylic acid *tert*-butyl ester



By proceeding in a manner similar to Reference Example 20(a) but using 4-chloro-3-(2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester [Reference Example 21(c)] there was prepared 4-chloro-3-formyl-indazole-1-carboxylic acid *tert*-butyl ester (0.217g) as a brown oil.

LC-MS (METHOD B): R_T = 3.49 minutes; 283 (M+H)⁺.

(d) 5-Ethoxy-3-formyl-indazole-1-carboxylic acid *tert*-butyl ester

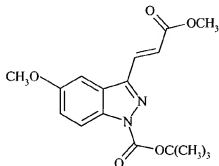


By proceeding in a manner similar to Reference Example 20(a) but using 5-ethoxy-3-(2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester [Reference Example 21(d)] there was prepared 5-ethoxy-3-formyl-indazole-1-carboxylic acid *tert*-butyl ester as a brown oil. TLC(ethyl acetate:hexane, 1:9, v/v): R_F = 0.25. ¹H NMR (400MHz, CDCl₃): δ 1.38(3H, t), 1.67(9H, s), 4.05(2H,

20 q), 7.12(1H, d), 7.60(1H, s), 7.98(1H, d), 10.20(1H, s).

REFERENCE EXAMPLE 21

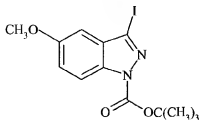
- (a) 5-Methoxy-3-(2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester



- 5 A solution of 3-iodo-5-methoxy-indazole-1-carboxylic acid *tert*-butyl ester [0.500g, Reference Example 22(a)] in dioxane (15ml) and under an atmosphere of nitrogen was treated with triethylamine (1.86ml) followed by methyl acrylate (1.20ml), triphenylphosphine (0.105g), and palladium (II) acetate (60mg). The resulting mixture was heated at 50°C for 16 hours, then cooled to ambient temperature and then evaporated. The residue was partitioned between ethyl acetate and water. The organic layer
- 10 was washed with brine, then dried over magnesium sulfate and then evaporated. The residue was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and 40/60 petrol (1:9, v/v) to yield 5-methoxy-3-(2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester (282mg). LC-MS (METHOD B): $R_T=3.33$ minutes; 333 (M+H)⁺.
- 15 (b) By proceeding in a manner similar to Reference Example 21(a) but using 4-fluoro-3-iodo-indazole-1-carboxylic acid *tert*-butyl ester [Reference Example 22(b)] there was prepared 4-fluoro-3-(2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester as a light brown solid. LC-MS (METHOD B): $R_T=3.39$ minutes; 321 (M+H)⁺.
- 20 (c) By proceeding in a manner similar to Reference Example 21(a) but using 4-chloro-3-iodo-indazole-1-carboxylic acid *tert*-butyl ester [Reference Example 22(c)] there was prepared 4-chloro-3-(2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester as a brown solid. LC-MS (METHOD B): $R_T=3.48$ minutes; 339 (M+H)⁺.
- 25 (d) By proceeding in a manner similar to Reference Example 21(a) but using 5-ethoxy-3-iodo-indazole-1-carboxylic acid *tert*-butyl ester [Reference Example 22(d)] there was prepared 5-ethoxy-3-(2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester as an off-white solid. LC-MS (METHOD B): $R_T=3.41$ minutes; 347 (M+H)⁺.

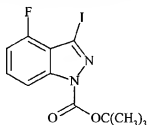
REFERENCE EXAMPLE 22

- (a) 3-Iodo-5-methoxy-indazole-1-carboxylic acid *tert*-butyl ester



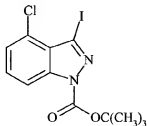
- A solution of 3-iodo-5-methoxy-1H-indazole [1.48g, Reference Example 23(a)] in acetonitrile (6ml) was treated with triethylamine (0.98ml) and N,N-dimethylaminopyridine (0.132g). The mixture was cooled to 0°C then treated with a solution of di-*tert*-butyl dicarbonate (1.41g) in acetonitrile (6ml). After stirring for 1 hour at ambient temperature the reaction mixture was evaporated and the residue was partitioned between ethyl acetate and water. The pH was adjusted to 2 and the organic layer was dried over magnesium sulfate and then evaporated. The residual orange oil was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and petrol (1:4, v/v) to yield 3-iodo-5-methoxy-indazole-1-carboxylic acid *tert*-butyl ester (1.72g) as a yellow solid.
- LC-MS (METHOD B): $R_T = 3.45$ minutes; 375 (M+H)⁺.

- (b) 4-Fluoro-3-iodo-indazole-1-carboxylic acid *tert*-butyl ester



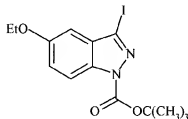
- By proceeding in a manner similar to Reference Example 22(a) above but using 4-fluoro-3-iodo-1H-indazole [Reference Example 23(b)] there was prepared 4-fluoro-3-iodo-indazole-1-carboxylic acid *tert*-butyl ester as a light brown solid. LC-MS (METHOD B): $R_T = 3.48$ minutes; 363 (M+H)⁺.

- (c) 4-Chloro-3-iodo-indazole-1-carboxylic acid *tert*-butyl ester



By proceeding in a manner similar to Reference Example 22(a) above but using 4-chloro-3-iodo-1H-indazole [Reference Example 23(c)] there was prepared 4-chloro-3-iodo-indazole-1-carboxylic acid *tert*-butyl ester as a brown solid. LC-MS (METHOD B): $R_T = 3.39$ minutes; 381 (M+H)⁺.

5 (d) 5-Ethoxy-3-iodo-indazole-1-carboxylic acid *tert*-butyl ester

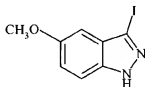


By proceeding in a manner similar to Reference Example 22(a) above but using 5-ethoxy-3-iodo-1H-indazole [Reference Example 23(d)] there was prepared 5-ethoxy-3-iodo-indazole-1-carboxylic acid *tert*-butyl ester as an off-white solid. LC-MS (METHOD B): $R_T = 3.49$ minutes; 389 (M+H)⁺.

10

REFERENCE EXAMPLE 23

(a) 3-Iodo-5-methoxy-1H-indazole



15 A solution of 5-methoxy-1H-indazole [0.815g, Reference Example 24(a)] in dimethyl formamide (8ml) was treated with iodine (2.80g) and potassium hydroxide (1.16g). The mixture was stirred at ambient temperature for 1 hour then poured into 10% aqueous sodium bisulfite solution (200ml) and then extracted three times with ethyl acetate. The combined organic extracts were washed with water, then with brine, then dried over magnesium sulfate and then evaporated to yield 3-iodo-5-methoxy-1H-indazole (1.48g) as a yellow solid. LC-MS (METHOD B): $R_T = 2.96$ minutes; 275 (M+H)⁺.

20

(b) 4-Fluoro-3-iodo-1H-indazole



By proceeding in a manner similar to Reference Example 23(a) above but using 4-fluoro-1H-indazole [Reference Example 24(b)] there was prepared 4-fluoro-3-iodo-1H-indazole as a red solid.

LC-MS (METHOD B): $R_T = 3.06$ minutes; 281 (M+H)⁺.

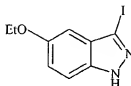
(c) 4-Chloro-3-iodo-1H-indazole



- 5 By proceeding in a manner similar to Reference Example 23(a) above but using 4-chloro-1H-indazole [Reference Example 24(c)] there was prepared 4-chloro-3-iodo-1H-indazole as a light brown solid.

LC-MS (METHOD B): $R_T = 2.97$ minutes; 263 (M+H)⁺.

(d) 5-Ethoxy-3-iodo-1H-indazole



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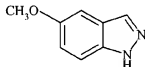
By proceeding in a manner similar to Reference Example 23(a) above but using 5-ethoxy-1H-indazole [Reference Example 37] there was prepared 5-ethoxy-3-iodo-1H-indazole as a light brown solid.

LC-MS (METHOD B): $R_T = 2.97$ minutes; 263 (M+H)⁺.

15

REFERENCE EXAMPLE 24

(a) 5-Methoxy-1H-indazole



20

A solution of 4-methoxy-2-methylaniline (2ml) in dichloromethane (10ml) was treated with triethylamine (3.27ml). The mixture was cooled to 0°C then treated with acetic anhydride (2.38ml), then stirred at ambient temperature for 1 hour, then cooled to 0°C when a pink solid precipitated. This solid was filtered, then washed with cold dichloromethane and then dissolved in acetic acid (55ml) and concentrated hydrochloric acid (20ml). This solution was cooled to -5°C, then treated with a solution of sodium nitrite (2.68g) in water (20ml), then stirred at that temperature for 1 hour and then treated with water (100ml). This mixture was stirred vigorously at 0°C for 10 minutes after which a yellow solid precipitated. This solid was filtered, then washed with water and then dissolved in toluene (13ml). This solution was heated to 80°C for 1.5 hours, then cooled and then washed with aqueous 1N

25

sodium carbonate solution. The organic phase was extracted three times with aqueous 2N hydrochloric acid and the acid extracts chilled and then made alkaline by addition of aqueous 5N sodium hydroxide solution. The aqueous layers were extracted three times with ethyl acetate and the combined organic layers were dried over magnesium sulfate and then evaporated to yield 5-methoxy-1H-indazole

5 (0.410g) as a yellow solid. LC-MS (METHOD B): $R_T = 1.32$ minutes; 149 (M+H)⁺.

(b) 4-Fluoro-1H-indazole



To tetrafluoroboric acid (8.2ml, 48 wt % in water) was added 3-fluoro-2-methylaniline (2.27ml). The mixture was cooled to 0°C when a precipitate formed which was redissolved by the addition of water (8ml). A solution of sodium nitrite (1.38g) in water (2.7ml) was then added dropwise and the mixture was then allowed to warm to ambient temperature and then stirred for a further 1 hour. The precipitated solid was filtered, then washed with diethyl ether, and then dried under suction for 30 minutes. The resulting tetrafluoroborate salt was added to a suspension of potassium acetate (3.92g) and 18-crown-6 (0.264g) in chloroform (45ml). After stirring for 3 hours at ambient temperature the bright orange mixture was filtered and the insoluble material was washed with dichloromethane, then subjected to flash column chromatography on silica eluting with a mixture of 40/60 petrol and ethyl acetate (3:1 v/v) to give 4-fluoro-1H-indazole (0.675g) as an off-white solid. LC-MS (METHOD B): $R_T = 2.70$ minutes; 137 (M+H)⁺.

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(c) 4-Chloro-1H-indazole



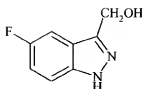
By proceeding to a manner similar to Reference Example 24(a) above but using 3-chloro-2-methylaniline, there was prepared 4-chloro-1H-indazole as a red solid (0.807g) which was used without further purification. LC-MS (METHOD B): $R_T = 2.90$ minutes; 155 (M+H)⁺.

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REFERENCE EXAMPLE 25

(a) (5-fluoro-1H-indazol-3-yl)-methanol

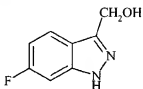
-497-



- A solution of 5-fluoro-1H-indazole-3-carboxylic acid [0.680g, Reference Example 26(a)] in anhydrous tetrahydrofuran (15ml), at 0°C, was treated portionwise with lithium aluminium hydride (0.716g), then stirred for 2 hours at ambient temperature and then treated with saturated aqueous sodium sulfate. The reaction mixture was acidified by addition of hydrochloric acid (1N) and then extracted three times with ethyl acetate (30ml). The combined organic extracts were dried over magnesium sulfate and then evaporated. The residual dark brown oil was subjected to flash column chromatography on silica eluting with a mixture of 40/60 petrol and ethyl acetate (1:1 to 1:3 v/v) to yield (5-fluoro-1H-indazol-3-yl)-methanol (0.144g) as a brown solid. LC-MS (METHOD B): $R_T = 2.40$ minutes; 167 (M+H)⁺.

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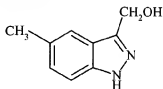
- (b) (6-Fluoro-1H-indazol-3-yl)-methanol



- By proceeding in a manner similar to Reference Example 25(a) above but using 6-fluoro-1H-indazole-3-carboxylic acid [Reference Example 26(b)] there was prepared (6-fluoro-1H-indazol-3-yl)-methanol (0.265g) as a dark grey solid. LC-MS (METHOD B): $R_T = 2.40$ minutes, 165 (M-H).

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- (c) (5-Methyl-1H-indazol-3-yl)-methanol

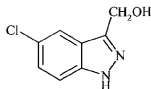


- By proceeding in a manner similar to Reference Example 25(a) above but using 5-methyl-1H-indazole-3-carboxylic acid [Reference Example 26(c)] there was prepared (5-methyl-1H-indazol-3-yl)-methanol (0.511g) as a brown oil. LC-MS (METHOD B): $R_T = 2.45$ minutes; 163 (M+H)⁺.

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- (d) (5-Chloro-1H-indazol-3-yl)-methanol

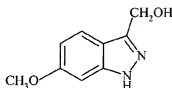
-498-



By proceeding in a manner similar to Reference Example 25(a) above but using 5-chloro-1H-indazole-3-carboxylic acid [Reference Example 26(d)] there was prepared (5-chloro-1H-indazol-3-yl)-methanol as a dark brown oil which solidified on standing. LC-MS (METHOD B): $R_T = 2.51$ minutes; 185

5 (M+H)⁺.

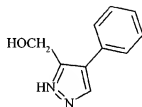
(e) (6-Methoxy-1H-indazol-3-yl)-methanol



By proceeding in a manner similar to Reference Example 25(a) above but using 6-methoxy-1H-indazole-3-carboxylic acid [Reference Example 26(e)] there was prepared (6-methoxy-1H-indazol-3-yl)-methanol (0.265g) as a brown solid. LC-MS (METHOD B): $R_T = 2.37$ minutes; 179 (M+H)⁺.

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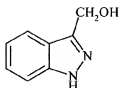
(f) (4-Phenyl-1H-pyrazol-3-yl)-methanol



15 By proceeding in a manner similar to Reference Example 25(a) above but using 4-phenyl-1H-pyrazole-3-carboxylic acid [Reference Example 47] and subjecting the reaction product to flash column chromatography on silica eluting with a mixture of dichloromethane and methanol (9:1, v/v) there was prepared (4-phenyl-1H-pyrazol-3-yl)-methanol. LC-MS (METHOD B): $R_T = 2.51$ minutes; 175 (M+H)⁺.

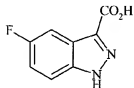
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(g) (1H-indazol-3-yl)-methanol

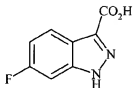


By proceeding in a manner similar to Reference Example 25(a) above but using indazole-3-carboxylic acid and subjecting the reaction product to column chromatography on silica eluting with a mixture of a mixture of *n*-hexane and ethyl acetate (1:1) to ethyl acetate there was prepared (1H-indazol-3-yl)-methanol as a pale yellow solid. LC-MS (METHOD B): $R_T = 3.17$ minutes; $149.21 ([M+H]^+)$.

5

REFERENCE EXAMPLE 26(a) 5-Fluoro-1H-indazole-3-carboxylic acid

- 10 A solution of 5-fluoroisatin (2g) and sodium hydroxide (0.509g) in water (20ml) was heated to 50°C for 30 minutes, then cooled and then treated with sodium nitrite (0.836g). This mixture was added over 10 minutes to a solution of concentrated sulfuric acid (2.26g) in water (200ml), at 0°C, whilst maintaining the temperature below 5°C. After a further 15 minutes a solution of tin (II) chloride (5.51g) in concentrated hydrochloric acid (10.5ml) was added and the resulting mixture maintained at 5°C for a further 30 minutes. The mixture was then stirred for a further 1 hour whilst warming to
- 15 ambient temperature then filtered. The light brown paste was dissolved in ethyl acetate and the solution was dried over magnesium sulfate and then evaporated to yield 5-fluoro-1H-indazole-3-carboxylic acid (0.863g) as a light brown solid which was used without further purification.
- LC-MS (METHOD B): $R_T = 2.51$ minutes; $181 (M+H)^+$.

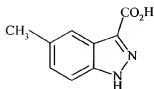
20 (b) 6-Fluoro-1H-indazole-3-carboxylic acid

By proceeding in a manner similar to Reference Example 26(a) above but using 6-fluoro-1H-indole-2,3-dione [Reference Example 27(a)] there was prepared 6-fluoro-1H-indazole-3-carboxylic acid (1.962g) as a light brown solid. LC-MS (METHOD B): $R_T = 2.50$ minutes; $181 (M+H)^+$.

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(c) 5-Methyl-1H-indazole-3-carboxylic acid

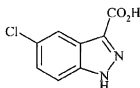
-500-



By proceeding in a manner similar to Reference Example 26(a) above but using 5-methyl isatin there was prepared 5-methyl-1H-indazole-3-carboxylic acid as a light brown solid. LC-MS (METHOD B): $R_T = 2.53$ minutes; 177 (M+H)⁺.

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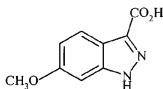
(d) 5-Chloro-1H-indazole-3-carboxylic acid



By proceeding in a manner similar to Reference Example 26(a) above but using 5-chloro isatin there was prepared 5-chloro-1H-indazole-3-carboxylic acid as a light brown solid. LC-MS (METHOD B):

10 $R_T = 2.58$ minutes; 171 (M+H)⁺.

(e) 6-Methoxy-1H-indazole-3-carboxylic acid

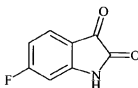


By proceeding in a manner similar to Reference Example 26(a) above but using 6-methoxy-1H-indole-2,3-dione [2.50g, Reference Example 27(b)] there was prepared 6-methoxy-1H-indazole-3-carboxylic acid as a light brown solid. LC-MS (METHOD B): $R_T = 2.45$ minutes; 193 (M+H)⁺.

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REFERENCE EXAMPLE 27

(a) 6-Fluoro-1H-indole-2,3-dione

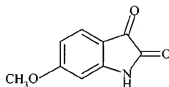


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To vigorously stirring polyphosphoric acid (100g) at 75°C was added N-(3-fluoro-phenyl)-2-hydroxyimino-acetamide [10.304g, Reference Example 28(a)] portionwise over 30 minutes. The resulting mixture was stirred at 80°C for 15 minutes, then poured into ice, then left to stand for 16

- hours and then filtered to give a brown paste. The filtrate was extracted four times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate and then evaporated. The residue and the brown paste from the filtration above were combined and treated with aqueous sodium hydroxide (1N). The mixture was filtered and the filtrate was acidified by addition of aqueous hydrochloric acid (2N). The resulting brown solid was filtered and then treated with aqueous sodium hydroxide (1N). This mixture was filtered and the filtrate was acidified by addition of aqueous hydrochloric acid (2N) and then filtered. The combined acidic aqueous filtrates were extracted four times with ethyl acetate, then dried over magnesium sulfate, and then evaporated to give 6-fluoro-1H-indole-2,3-dione (1.861g) as a pale orange solid. LC-MS (METHOD B): R_T = 2.49 minutes; 166 (M+H)⁺.

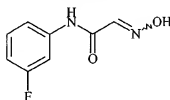
(b) 6-Methoxy-1H-indole-2,3-dione



- By proceeding in a manner similar to Reference Example 27(a) above but using 2-hydroxyimino-N-(3-methoxy-phenyl)-acetamide [7.20g, Reference Example 28(b)] there was prepared 6-methoxy-1H-indole-2,3-dione as a brown solid. LC-MS (METHOD B): R_T = 2.49 minutes; 178 (M+H)⁺.

REFERENCE EXAMPLE 28

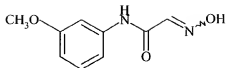
(a) N-(3-Fluoro-phenyl)-2-hydroxyimino-acetamide



- A mixture of chloral hydrate (0.819g) in water (25ml) was treated with sodium sulfate (5.10g), 3-fluoroaniline (0.43ml), concentrated hydrochloric acid (0.3ml), and hydroxylaminic hydrochloride (0.938g). The mixture was warmed to 80°C for 2 hours then allowed to cool and then filtered. The solid was washed with water and then dried in air for 16 hours to afford N-(3-fluoro-phenyl)-2-hydroxyimino-acetamide (0.756g) as a buff solid. LC-MS (METHOD B): R_T = 2.51 minutes; 181 (M+H)⁺.

(b) 2-Hydroxyimino-N-(3-methoxy-phenyl)-acetamide

-502-

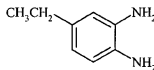


By proceeding in a manner similar to Reference Example 28(a) above but using m-anisidine (0.5ml) there was prepared 2-hydroxyimino-N-(3-methoxy-phenyl)-acetamide as a brown solid. LC-MS (METHOD B): $R_T = 2.44$ minutes; $195 (M+H)^+$.

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REFERENCE EXAMPLE 29

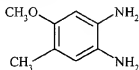
(a) 4-Ethyl-phenylene diamine



A stirred solution of 5-ethyl-2-nitro-aniline [200 mg, Reference Example 30(a)] and tin chloride (2.75 g) in ethanol (5 ml) was heated in a Smith Creator microwave at 140°C for 10 minutes. The reaction mixture was basified to pH 8 by addition of saturated sodium hydrogen carbonate solution and then extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and then evaporated to give 4-ethyl-phenylene diamine (140 mg) as a pale orange solid, which was used without future purification. MS: $137.2 (M+H)^+$. HPLC (METHOD H): $R_T = 2.91$ minutes.

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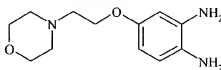
(b) 4-Methoxy-5-methyl-benzene-1,2-diamine



By proceeding in a manner similar to Reference Example 29(a) above but using 4-methoxy-5-methyl-2-nitro-phenylamine [582mg, Reference Example 31(i)] there was prepared 4-methoxy-5-methyl-benzene-1,2-diamine (454mg) as a light brown solid. LC-MS (Method K): $R_T = 2.39$ minutes, $153.20 (M+H)^+$.

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(c) 4-(2-Morpholin-4-yl-ethoxy)-benzene-1,2-diamine



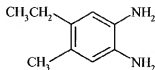
By proceeding in a manner similar to Reference Example 29(a) above but using 4-[2-(3,4-dinitro-phenoxy)-ethyl]-morpholine [Reference Example 67] there was prepared 4-(2-morpholin-4-yl-ethoxy)-

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benzene-1,2-diamine (170mg) as a pale brown oil. LC-MS (METHOD N): $R_T = 2.2$ minutes, 238.21 (M+H)⁺.

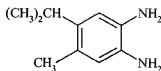
REFERENCE EXAMPLE 30

- 5 (a) 4-Ethyl-5-methyl-phenylene diamine



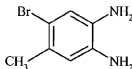
- A stirred solution of 4-ethyl-5-methyl-2-nitro-aniline [484 mg, Reference Example 31(b)] in methanol (20 ml) was treated with tin chloride (5.09 g), then heated at reflux for 16 hours and then cooled to ambient temperature. The pH of the reaction mixture was adjusted to pH 8 by addition of aqueous sodium bicarbonate and then this mixture was extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and then evaporated to give 4-ethyl-5-methyl-phenylene diamine (374 mg) as an off-white solid. LC-MS (METHOD B): $R_T = 1.80$ minutes; 151.25 (M+H)⁺.
- 10

- (b) 4-Isopropyl-5-methyl-phenylene diamine



- By proceeding in a manner similar to Reference Example 30(a) above but using 4-isopropyl-5-methyl-2-nitro-aniline [Reference Example 31(c)] there was prepared 4-isopropyl-5-methyl-phenylene diamine as a light brown solid. LC-MS (Method C): $R_T = 3.30$ minutes; 165.16 (M+H)⁺.
- 15

- 20 (c) 4-Bromo-5-methyl-phenylene diamine

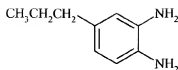


By proceeding in a manner similar to Reference Example 30(a) above but using 4-bromo-5-methyl-2-nitro-aniline [Reference Example 31(d)] there was prepared 4-bromo-5-methyl-phenylene diamine as an off-white solid. LC-MS (METHOD B): $R_T = 2.63$ minutes; 203.22 (M+H)⁺.

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- (d) 4-n-propyl-phenylene diamine

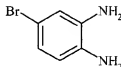
-504-



By proceeding in a manner similar to Reference Example 30(a) above but using 4-n-propyl-2-nitro-aniline [Reference Example 31(e)] there was prepared 4-n-propyl-phenylene diamine as an off-white solid. LC-MS (METHOD B): $R_T = 2.07$ minutes; 151.30 (M+H)⁺.

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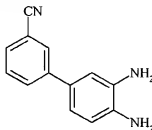
(c) 4--Bromo-phenylene diamine



By proceeding in a manner similar to Reference Example 30(a) above but using 4-bromo-2-nitro-aniline there was prepared 4-bromo-phenylene diamine as a yellow solid. LC-MS (METHOD B): $R_T = 1.77$ minutes; 187.22 (M+H)⁺.

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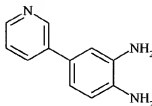
(f) 3',4'-diaminobiphenyl-3-carbonitrile



By proceeding in a manner similar to Reference Example 30(a) above but using 4'-amino-3'-nitro-biphenyl-3-carbonitrile [Reference Example 34(a)] there was prepared 3',4'-diaminobiphenyl-3-carbonitrile as an off-white solid. LC-MS (METHOD B): $R_T = 2.72$ minutes; 210.3 (M+H)⁺.

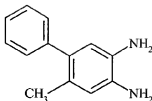
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(g) 4-(pyridine-3-yl)benzene-1,2-diamine

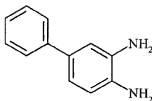


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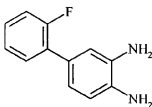
By proceeding in a manner similar to Reference Example 30(a) above but using 2-nitro-4-pyridine-3-yl-phenylamine [Reference Example 34(b)] there was prepared 4-(pyridine-3-yl)benzene-1,2-diamine as an off-white solid. LC-MS (METHOD B): $R_T = 0.37$ minutes; 186.3 (M+H)⁺.

(h) 6-methylbiphenyl-3,4-diamine

- By proceeding in a manner similar to Reference Example 30(a) above but using 2-methyl-5-nitro-biphenyl-4-ylamine [Reference Example 34(c)] there was prepared 6-methylbiphenyl-3,4-diamine as an off-white solid. LC-MS (METHOD B): $R_T = 2.36$ minutes; 199.25 (M+H)⁺.

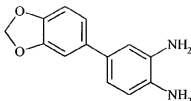
(i) biphenyl-3,4-diamine

- 10 By proceeding in a manner similar to Reference Example 30(a) above but using 3-nitrobiphenyl-4-ylamine [Reference Example 34(d)] there was prepared biphenyl-3,4-diamine as a yellow solid. LC-MS (METHOD B): $R_T = 2.25$ minutes; 185.3 (M+H)⁺.

(j) 2'-fluorobiphenyl-3,4-diamine

- 15 By proceeding in a manner similar to Reference Example 30(a) above but using 2'-fluoro-3-nitro-biphenyl-4-ylamine [Reference Example 34(e)] there was prepared 2'-fluorobiphenyl-3,4-diamine as a white solid. LC-MS (METHOD B): $R_T = 2.73$ minutes; 203.31 (M+H)⁺.

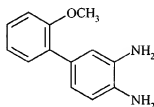
- 20 (k) 4-benzo[1,3]dioxol-5-ylbenzene-1,2-diamine



By proceeding in a manner similar to Reference Example 30(a) above but using 4-benzo[1,3]dioxo-5-yl-2-nitrophenylamine [Reference Example 34(f)] there was prepared 4-benzo[1,3]dioxol-5-ylbenzene-1,2-diamine as a white solid. LC-MS (METHOD B): $R_T = 2.66$ minutes; 229.3 (M+H)⁺.

5

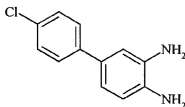
(l) 2'-methoxybiphenyl-3,4-diamine



By proceeding in a manner similar to Reference Example 30(a) above but using 2'-methoxy-3-nitro-biphenyl-4-ylamine [Reference Example 34(g)] there was prepared 2'-methoxybiphenyl-3,4-diamine as a white solid. LC-MS (METHOD B): $R_T = 2.74$ minutes; 215.33 (M+H)⁺.

10

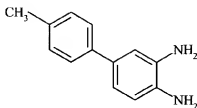
(m) 4'-chlorobiphenyl-3,4-diamine



By proceeding in a manner similar to Reference Example 30(a) above but using 4'-chloro-3-nitro-biphenyl-4-ylamine [Reference Example 34(h)] there was prepared 4'-chlorobiphenyl-3,4-diamine as a white solid. LC-MS (METHOD B): $R_T = 2.85$ minutes; 219.3 (M+H)⁺.

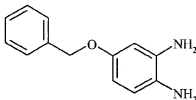
15

(n) 4'-methylbiphenyl-3,4-diamine



By proceeding in a manner similar to Reference Example 30(a) above but using 4'-methyl-3-nitro-biphenyl-4-yl-amine [Reference Example 34(i)] there was prepared 4'-methylbiphenyl-3,4-diamine as a white solid. LC-MS (METHOD B): $R_T = 2.39$ minutes, 199.25 (M+H)⁺.

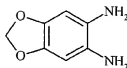
5 (o) 4-benzyloxybenzene-1,2-diamine



By proceeding in a manner similar to Reference Example 30(a) above but using 4-benzyloxy-1,2-dinitrobenzene [Reference Example 35(a)] there was prepared 4-benzyloxybenzene-1,2-diamine as a white solid. LC-MS (METHOD B): $R_T = 2.34$ minutes, 215.33 (M+H)⁺.

10

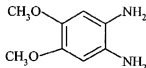
(p) benzo[1,3]dioxole-5,6-diamine



By proceeding in a manner similar to Reference Example 30(a) above but using 5,6-dinitro-benzo[1,3]dioxole [Reference Example 56(b)] there was prepared benzo[1,3]dioxole-5,6-diamine as an

15 oily solid. LC-MS (METHOD B): $R_T = 0.43$ minutes, 153.18 (M+H)⁺.

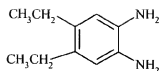
(q) 4,5-dimethoxybenzene-1,2-diamine



20 By proceeding in a manner similar to Reference Example 30(a) above but using 4,5-dimethoxy-2-nitroaniline there was prepared 4,5-dimethoxybenzene-1,2-diamine as an oily solid. LC-MS (METHOD B): $R_T = 0.43$ minutes, 169.24 (M+H)⁺.

(r) 4,5-diethylbenzene-1,2-diamine

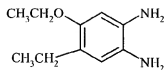
-508-



By proceeding in a manner similar to Reference Example 30(a) above but using 4,5-diethyl-2-nitroaniline [Reference Example 31(f)] there was prepared 4,5-diethylbenzene-1,2-diamine which was used without further purification. LC-MS (METHOD B): $R_T = 2.21$ minutes, 165.24 ($M+H$) $^+$.

5

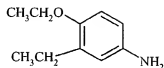
(s) 4-ethoxy-5-ethylbenzene-1,2-diamine



By proceeding in a manner similar to Reference Example 30(a) above but using 4-ethoxy-5-ethyl-2-nitrophenylamine [Reference Example 31(g)] there was prepared 4-ethoxy-5-ethylbenzene-1,2-diamine.

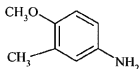
10

(t) 4-Ethoxy-3-ethyl-phenylamine



15 By proceeding in a manner similar to Reference Example 30(a) above but using 1-ethoxy-2-ethyl-4-nitrobenzene [Reference Example 32(h)] and subjecting the reaction product to chromatography on silica gel (heptane, ethyl acetate gradient 25-35%) there was prepared 4-ethoxy-3-ethyl-phenylamine (0.6 g) as an oil. GS-MS one peak, $R_T = 7.17$ minutes. MS 165 (M) $^+$.

20 (u) 4-Methoxy-3-methyl-phenylamine

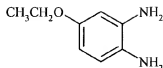


By proceeding in a manner similar to Reference Example 30(a) above but using 1-methoxy-2-methyl-4-nitrobenzene [2.7g, Reference Example 56(a)] there was prepared 4-methoxy-3-methyl-phenylamine (2.07g). $R_F = 0.5$ [ethyl acetate/n-pentane, 1:1, v/v].

25

(v) 4-Ethoxy-benzene-1,2-diamine

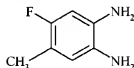
-509-



By proceeding in a manner similar to Reference Example 30(a) above but using 4-ethoxy-2-nitroaniline (1.5g) 4-ethoxy-benzene-1,2-diamine (1.02g) as a brown oil. LC-MS (Method J): $R_T = 0.50$ and 3.88 minutes, 153.30 (M+H)⁺.

5

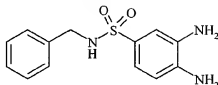
(w) 4-Fluoro-5-methyl-benzene-1,2-diamine



By proceeding in a manner similar to Reference Example 30(a) above but using 4-fluoro-5-methyl-2-nitro-phenylamine [Reference Example 31(j)] there was prepared 4-fluoro-5-methyl-benzene-1,2-

10 diamine (1.27g) as a yellow solid. LC-MS (METHOD J): $R_T = 1.93$ minutes, 141.25 (M+H)⁺.

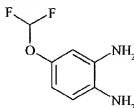
(x) 3,4-Diamino-N-benzyl-benzenesulfonamide



By proceeding in a manner similar to Reference Example 30(a) above but using 4-amino-N-benzyl-3-nitro-benzenesulfonamide [Reference Example 61] there was prepared 3,4-diamino-N-benzyl-benzenesulfonamide (0.350g) as a yellow film. LC-MS (METHOD K): $R_T = 2.87$ minutes, 278.28 (M+H)⁺.

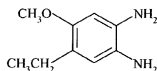
15

(y) 4-Difluoromethoxy-benzene-1,2-diamine



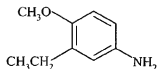
By proceeding in a manner similar to Reference Example 30(a) above but using 4-difluoromethoxy-2-nitro-phenylamine [Reference Example 31(k)] there was prepared 4-difluoromethoxy-benzene-1,2-
 20 diamine (2.70g) as a pale brown solid. LC-MS (METHOD N): $R_T = 2.45$ minutes, 175 (M+H)⁺.

- (z) 4-Ethyl-5-methoxy-benzene-1,2-diamine [200 mg, Reference Example 30(z)]



- 5 By proceeding in a manner similar to Reference Example 30(a) but using 5-ethyl-4-methoxy-2-nitro-phenylamine [2.4 g, Reference Example 31(l)] there was prepared 4-ethyl-5-methoxy-benzene-1,2-diamine (1.6 g) as a black solid. LC-MS (METHOD I, AMMONIUM ACETATE, 5min): $R_T = 3.50$ minutes, 167.17 (M+H)⁺.

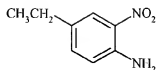
- 10 (aa) 3-Ethyl-4-methoxy-phenylamine



- By proceeding in a manner similar to Reference Example 30(a) but using 5-ethyl-4-methoxy-2-nitro-phenylamine [3.6g, Reference Example 31(l)] and carrying out the reaction for 24 hours, there was prepared 3-ethyl-4-methoxy-phenylamine (2.5g) as a brown oil. LC-MS (METHOD J): $R_T = 2.04$ minutes, 152.2 (M+H)⁺.

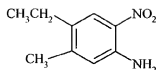
REFERENCE EXAMPLE 31

- (a) 5-Ethyl-2-nitro-aniline



- 20 A stirred solution of sodium methoxide (0.35 g) in methanol (15 ml) was treated with a solution of 4-ethyl-2-nitro-*N*-acetyl-aniline [1g, Reference Example 32(a)] in methanol (15 ml). The reaction mixture was stirred at room temperature for 24 hours and then poured onto ice-water. The resulting precipitate was filtered and then dried to give 5-ethyl-2-nitro-aniline (650 mg). LC-MS (METHOD B): $R_T = 3.11$ minutes; 167.2 (M+H)⁺.
- 25 (b) 4-Ethyl-5-methyl-2-nitro-aniline

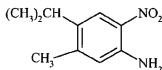
-511-



By proceeding in a manner similar to Reference Example 31(a) above but using 4-ethyl-5-methyl-2-nitro-*N*-acetyl-aniline [1g, Reference Example 32(b)] there was prepared 4-ethyl-5-methyl-2-nitro-aniline as an orange solid. LC-MS (METHOD B): $R_T = 3.16$ minutes; 181.14 (M+H)⁺.

5

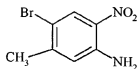
(c) 4-isopropyl-5-methyl-2-nitro-aniline



By proceeding in a manner similar to Reference Example 31(a) above but using 4-isopropyl-5-methyl-2-nitro-*N*-acetyl-aniline [1g, Reference Example 32(c)] there was prepared 4-isopropyl-5-methyl-2-

10 nitro-aniline as an orange solid. LC-MS (METHOD B): $R_T = 3.26$ minutes; 195.3 (M+H)⁺.

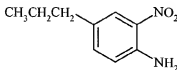
(d) 4-bromo-5-methyl-2-nitro-aniline



By proceeding in a manner similar to Reference Example 31(a) above but using 4-bromo-5-methyl-2-nitro-*N*-acetyl-aniline [1g, Reference Example 32(d)] there was prepared 4-bromo-5-methyl-2-nitro-

15 aniline as a brown solid. LC-MS (METHOD B): $R_T = 3.24$ minutes; 231.2 (M+H)⁺.

(e) 4-n-Propyl-2-nitro-aniline

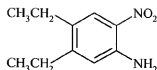


20 By proceeding in a manner similar to Reference Example 31(a) above but using 2-nitro-4-propyl-*N*-acetyl-aniline there was prepared 4-n-propyl-2-nitro-aniline as an orange solid.

LC-MS (Method C): $R_T = 3.46$ minutes; 181.2 (M+H)⁺.

(f) 4,5-diethyl-2-nitro-aniline

-512-

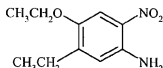


By proceeding in a manner similar to Reference Example 31(a) above but using 4,5-diethyl-2-nitro-*N*-acetyl-aniline [Reference Example 32(f)] there was prepared 4,5-diethyl-2-nitro-aniline.

LC-MS (METHOD B): $R_T = 3.27$ minutes; $195.22 (M+H)^+$.

5

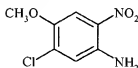
(g) 4-Ethoxy-5-ethyl-2-nitrophenylamine



N-(4-Ethoxy-5-ethyl-2-nitrophenyl)acetamide [0.2g, Reference Example 32(g)] was dissolved in ethanol (25 mL) and sodium hydride (100 mg, 50% dispersion in mineral oil, 2 mmol) was added.

- 10 Mixture was stirred overnight at ambient temperature, aq ammonium chloride (3 mL) was added and the mixture was evaporated. The residue was chromatographed on silica gel (heptane with gradient of 25-50% ethyl acetate) to give 4-ethoxy-5-ethyl-2-nitrophenylamine (0.1g) as a red solid. LC-MS (Method E): $R_T = 3.4$ minutes, $211 (M+H)^+$.

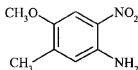
15 (h) 5-Chloro-4-methoxy-2-nitrophenylamine



N-(5-Chloro-4-methoxy-2-nitrophenyl)acetamide (8.0g, Reference Example 32(i)) was added to a solution of sodium methoxide (2.0g, 0.037 mole) in methanol (150 mL) and the mixture was stirred at ambient temperature for 4 hours. The reaction mixture was added to ice water (750 mL), stirred for 15

20 minutes and the aqueous mixture was filtered. The precipitate was washed with water and dried at 60°C under vacuum to give 5-chloro-4-methoxy-2-nitrophenylamine (6.52 g) as an orange solid, mp 128-129° C.

(i) 4-Methoxy-5-methyl-2-nitro-phenylamine

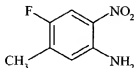


25

By proceeding in a manner similar to Reference Example 31(a) above but using *N*-(4-methoxy-5-

methyl-2-nitro-phenyl)-acetamide [2.53g, Reference Example 32(j)] there was prepared 4-methoxy-5-methyl-2-nitro-phenylamine (2.05g) as a bright orange solid. LC-MS (Method J): $R_T = 3.46$ minutes, 183.29 (M+H)⁺.

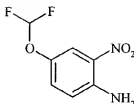
5 (j) 4-Fluoro-5-methyl-2-nitro-phenylamine



By proceeding in a manner similar to Reference Example 31 (a) above but using N-(4-fluoro-5-methyl-2-nitro-phenyl)-acetamide [2.53g, Reference Example 32(k)] there was prepared 4-fluoro-5-methyl-2-nitro-phenylamine (2.25g) as an orange solid. LC-MS (METHOD J): $R_T = 3.53$ minutes, 171.28

10 (M+H)⁺.

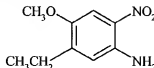
(k) 4-difluoromethoxy-2-nitro-phenylamine



By proceeding in a manner similar to Reference Example 31 (a) above but using N-(4-difluoromethoxy-

15 2-nitro-phenyl)-acetamide [Reference Example 32(l)] there was prepared 4-difluoromethoxy-2-nitro-phenylamine (10g) as an orange solid. LC-MS (METHOD N): $R_T = 3.86$ minutes, 205 (M+H)⁺.

(l) 5-Ethyl-4-methoxy-2-nitro-phenylamine



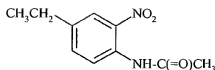
20 By proceeding in a manner similar to Reference Example 31 (a) but using N-(5-ethyl-4-methoxy-2-nitro-phenyl)-acetamide [2.4 g, Reference Example 32(m)] there was prepared 5-ethyl-4-methoxy-2-nitro-phenylamine (1.9 g) as a brown solid. LC-MS (METHOD K): $R_T = 4.14$ minutes, 197.09 (M+H)⁺.

25

REFERENCE EXAMPLE 32

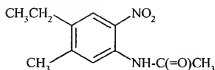
(a) 4-Ethyl-2-nitro-N-acetyl-aniline

-514-

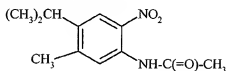


A stirred solution of 4-ethyl-*N*-acetyl-aniline [3g, Reference Example 33(a)] in acetic anhydride (8mL) and acetic acid (4mL), at -5°C , was treated dropwise with a mixture of acetic acid (1.75mL) and concentrated nitric acid (1.22mL). The mixture was warmed to 0°C , then stirred at 0°C for 2 hours and then poured onto water. This mixture was evaporated and the resulting oil was partitioned between ethyl acetate and water. The organic layer was dried over magnesium sulfate and then evaporated. The residual oil was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and petroleum ether (2:5) to give 4-ethyl-2-nitro-*N*-acetyl-aniline (1.4g) as an orange solid. LC-MS (METHOD B): $R_T = 2.95$ minutes; 209.2 (M+H) $^{+}$.

10

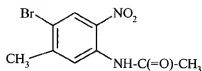
(b) 4-Ethyl-5-methyl-2-nitro-*N*-acetyl-aniline

By proceeding in a manner similar to Reference Example 32(a) above but using 3-methyl-4-ethyl-*N*-acetyl aniline there was prepared 4-ethyl-5-methyl-2-nitro-*N*-acetyl-aniline as a orange solid.

15 LC-MS (METHOD B): $R_T = 3.03$ minutes; 223.25 (M+H) $^{+}$.(c) 4-isopropyl-5-methyl-2-nitro-*N*-acetyl-aniline

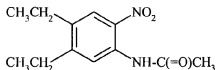
By proceeding in a manner similar to Reference Example 32(a) above but using 3-methyl-4-isopropyl-*N*-acetyl aniline [Reference Example 33(b)] there was prepared 4-isopropyl-5-methyl-2-nitro-*N*-acetyl-aniline as an orange solid. LC-MS (METHOD B): $R_T = 3.15$ minutes; 231.36 (M+H) $^{+}$.

20

(d) 4-Bromo-5-methyl-2-nitro-*N*-acetyl-aniline

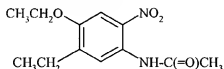
By proceeding in a manner similar to Reference Example 32(a) above but using 3-methyl-4-bromo-*N*-acetyl aniline [Reference Example 33(c)] there was prepared 4-bromo-5-methyl-2-nitro-*N*-acetyl-aniline as an orange solid. LC-MS (METHOD B): $R_T = 3.06$ minutes; 274.2 (M+H)⁺.

5 (f) 4,5-Diethyl-2-nitro-*N*-acetyl-aniline



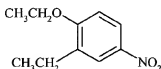
By proceeding in a manner similar to Reference Example 32(a) above but using 3,4-diethyl-*N*-acetyl aniline [Reference Example 33(d)] there was prepared 4,5-diethyl-2-nitro-*N*-acetyl-aniline as an orange
10 solid. LC-MS (METHOD B): $R_T = 3.18$ minutes; 237.4 (M+H)⁺.

(g) *N*-(4-Ethoxy-5-ethyl-2-nitrophenyl)acetamide



N-(4-Ethoxy-3-ethyl-phenyl) acetamide [3.1g, Reference Example 33(e)] was dissolved in acetic
15 anhydride (5 mL), a solution of nitric acid in acetic acid (0.5mL of 95% nitric acid, in 4mL) was added and the mixture was stirred overnight at ambient temperature. The mixture was diluted with water (100mL) and the aqueous mixture was extracted twice with ethyl acetate (100mL). The combined extracts were evaporated and the residue was chromatographed on silica gel (heptane/ethyl acetate 9/1) to give *N*-(4-ethoxy-5-ethyl-2-nitrophenyl)acetamide (3.0 g) as a bright yellow solid. LC-
20 MS (Method E): $R_T = 3.27$ minutes, 253 (M+H)⁺.

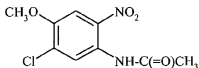
(h) 1-Ethoxy-2-ethyl-4-nitrobenzene



A solution of 1-ethoxy-2-ethyl benzene (3.5g, Reference Example 51) in acetic anhydride (30 mL) was
25 chilled in an ice-water bath. A solution of nitric acid (1.4 mL of 90% - 30% excess) in acetic acid (25 mL) was added dropwise and the mixture was stirred overnight at ambient temperature. The reaction mixture was poured into ice water (300 mL) and the aqueous mixture was extracted with ethyl acetate (2 X 200 mL). The combined extracts were evaporated and the residue was chromatographed on silica

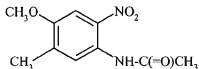
gel (heptane with gradient of 5 to 10% ethyl acetate) to give 1-ethoxy-2-ethyl-4-nitrobenzene (1.4 g) as a clear liquid. LC-MS (Method E) $R_T = 3.75$ minutes, 196 (M+H)⁺.

(i) N-(5-Chloro-4-methoxy-2-nitrophenyl)acetamide



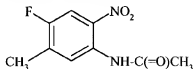
A solution of N-(3-chloro-4-methoxyphenyl)acetamide (6.85g, Reference Example) in a mixture of acetic acid (20 mL) and acetic anhydride (35 mL) was cooled to -5° C and a solution of fuming nitric acid (3 mL) in acetic acid (4 mL) was added dropwise keeping the reaction temperature below 0° C. The mixture was stirred at 0° C for 30 minutes at which point a yellow precipitate developed. After another 1.5 h at 0° C, the mixture was poured into water (100 mL) and the aqueous mixture was vigorously stirred for 15 minutes and filtered. The yellow precipitate was washed with water and dried under vacuum at 60° C to give the product (8.0g) as a yellow solid, mp 152-153° C. MS 245 (M+H)⁺.

(j) N-(4-Methoxy-5-methyl-2-nitro-phenyl)-acetamide



By proceeding in a manner similar to Reference Example 32(a) but using N-(4-methoxy-3-methyl-phenyl)-acetamide [2.65g, Reference Example 33(f)] there was prepared N-(4-methoxy-5-methyl-2-nitro-phenyl)-acetamide (2.53g) as a orange solid. LC-MS (Method J): $R_T = 3.30$ minutes, 225.29 (M+H)⁺, 223.29 (M-H)⁻.

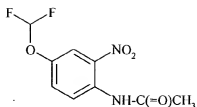
(k) N-(4-Fluoro-5-methyl-2-nitro-phenyl)-acetamide



By proceeding in a manner similar to Reference Example 32(a) above but using N-(4-fluoro-3-methyl-phenyl)-acetamide [2.65g, Reference Example 33(g)] there was prepared N-(4-fluoro-5-methyl-2-nitro-phenyl)-acetamide (2.25g) as a yellow solid. LC-MS (METHOD J): $R_T = 3.31$ minutes, 211.26 (M-H)⁻.

(l) N-(4-Difluoromethoxy-2-nitro-phenyl)-acetamide

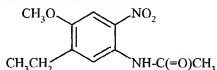
-517-



By proceeding in a manner similar to Reference Example 32(a) above but using N-(4-difluoromethoxy-phenyl)-acetamide [Reference Example 33(h)] there was prepared N-(4-difluoromethoxy-2-nitro-phenyl)-acetamide (450mg) as a yellow solid. LC-MS (METHOD K):

5 $R_T = 3.72$ minutes, MS: 245 (M-H)⁻.

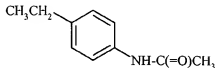
(m) N-(5-Ethyl-4-methoxy-2-nitro-phenyl)-acetamide



By proceeding in a manner similar to Reference Example 32(a) but using N-(3-ethyl-4-methoxy-phenyl)-acetamide [2.9 g, Reference Example 33(i)] there was prepared N-(5-Ethyl-4-methoxy-2-nitro-phenyl)-acetamide (2.4 g) as a yellow solid. LC-MS (METHOD K): $R_T = 4.04$ minutes, MS: 239.16 (M+H)⁺.

REFERENCE EXAMPLE 33

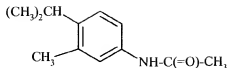
15 (a) 4-Ethyl-N-acetyl-aniline



A stirred solution of 4-ethylaniline (2g) and triethylamine (13.91mL) in dichloromethane (40mL) at 0°C under nitrogen was treated dropwise with acetic anhydride (4.67mL). The mixture was warmed to ambient temperature, then stirred for 16 hours at room temperature, then washed with (i) 10% citric acid (40mL), (ii) water (40mL) and (iii) brine (40mL). The organic phase was dried over magnesium sulfate and then evaporated to give 4-ethyl-N-acetyl-aniline (2.36g) as a pale orange solid which was used without further purification. LC-MS (METHOD B): $R_T = 2.80$ minutes; 164.2 (M+H)⁺.

20 (b) 3-Methyl-4-isopropyl-N-acetyl aniline

-518-

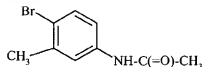


By proceeding in a manner similar to Reference Example 33(a) above but using 3-methyl-4-isopropylaniline there was prepared 3-methyl-4-isopropyl-N-acetyl aniline as an orange solid.

LC-MS (METHOD B): $R_T = 2.97$ minutes; 192.3 (M+H)⁺.

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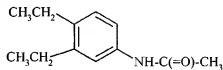
(c) 3-Methyl-4-bromo-N-acetyl aniline



By proceeding in a manner similar to Reference Example 33(a) above but using 3-methyl-4-bromoaniline there was prepared 3-methyl-4-bromo-N-acetyl aniline as a brown solid.

10 LC-MS (METHOD B): $R_T = 2.88$ minutes; 228.12 (M+H)⁺.

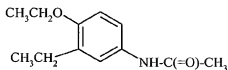
(d) 3,4-Diethyl-N-acetyl aniline



By proceeding in a manner similar to Reference Example 33(a) above but using 3,4-diethylaniline there was prepared 3,4-diethyl-N-acetyl aniline which was used without further purification.

LC-MS (METHOD B): $R_T = 3.03$ minutes; 192.30 (M+H)⁺.

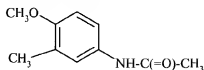
(e) N-(4-Ethoxy-3-ethyl-phenyl)acetamide



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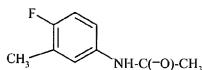
To a solution of 4-ethoxy-3-ethyl-phenylamine [0.6 g, Reference Example 30(t)] in pyridine (5mL) was added acetic anhydride (1mL) and the mixture was stirred 18 hours at ambient temperature. The reaction mixture was diluted with water (100mL) and the aqueous mixture was extracted twice with ethyl acetate (100mL). The combined extracts were evaporated to give N-(4-ethoxy-3-ethyl-phenyl)

25 acetamide (0.6g) as a pink foam. GC-MS one peak, $R_T = 9.16$ minutes, MS 207 (M)⁺.

(f) N-(4-Methoxy-3-methyl-phenyl)-acetamide

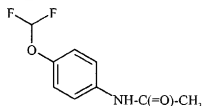
By proceeding in a manner similar to Reference Example 33(a) above but using 4-methoxy-3-methyl-phenylamine (2.07g, Reference Example 30(u)) and subjecting the reaction product to flash

- 5 chromatography on silica eluting with a mixture of ethyl acetate and n-pentane (1:1, v/v) there was prepared N-(4-methoxy-3-methyl-phenyl)-acetamide (2.65g) as a pale pink crystalline solid. LC-MS (Methd J): $R_T = 2.94$ minutes, 180.30 (M+H)⁺.

(g) N-(4-Fluoro-3-methyl-phenyl)-acetamide

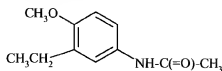
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By proceeding in a manner similar to Reference Example 33(a) above but using 4-fluoro-3-methylaniline there was prepared N-(4-fluoro-3-methyl-phenyl)-acetamide (3.82 g) as an orange solid. LC-MS (METHOD J): $R_T = 3.08$ minutes, 168.24 (M+H)⁺.

15 (h) N-(4-Difluoromethoxy-phenyl)-acetamide

By proceeding in a manner similar to Reference Example 33(a) above but using 4-difluoromethoxyaniline there was prepared N-(4-difluoromethoxy-phenyl)-acetamide (5.90 g) as an orange solid. LC-MS (METHOD K): $R_T = 3.62$ minutes, 202 (M+H)⁺.

20

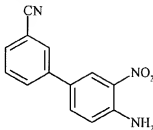
(i) N-(3-Ethyl-4-methoxy-phenyl)-acetamide

By proceeding in a manner similar to Reference Example 33(a) but using 3-ethyl-4-methoxy-phenylamine [2.5g, Reference Example 30(aa)] there was prepared N-(3-ethyl-4-methoxy-phenyl)-

acetamide (2.9 g) was prepared as a light brown solid. LC-MS (METHOD K): $R_T = 3.92$ minutes, 194.16 (M+H)⁺.

REFERENCE EXAMPLE 34

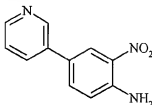
5 (a) 4'-Amino-3'-nitro-biphenyl-3-carbonitrile



A stirred solution of 3-cyanophenyl boronic acid (812mg) and tetrakis(triphenylphosphine) palladium (150mg) in tetrahydrofuran (4mL) under at atmosphere of nitrogen was treated with 4-bromo-2-nitroaniline in tetrahydrofuran (10mL). The reaction mixture was heated at 85°C for 48 hours, then
 10 cooled to ambient temperature and then partitioned between ethyl acetate and water. The organic layer was washed with brine, then dried over magnesium sulfate and then evaporated. The residue was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and hexane (1:2,v/v) to give 4'-amino-3'-nitro-biphenyl-3-carbonitrile (224mg) as a yellow solid. LC-MS (METHOD B): $R_T = 3.21$ minutes, 240.3 (M+H)⁺.

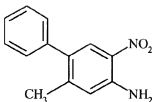
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(b) 2-nitro-4-pyridine-3-yl-phenylamine



By proceeding in a manner similar to Reference Example 34(a) above but using pyridine-3-boronic acid there was prepared 2-nitro-4-pyridine-3-yl-phenylamine as a yellow solid. LC-MS (METHOD B):
 20 $R_T = 2.09$ minutes, 216.24 (M+H)⁺.

(c) 2-methyl-5-nitro-biphenyl-4-yl amine

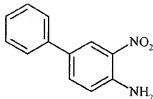


By proceeding in a manner similar to Reference Example 34(a) above but using phenyl boronic acid and 4-bromo-5-methyl-2-nitro-aniline [Reference Example 31(d)] there was prepared 2-methyl-5-nitro-biphenyl-4-yl amine as an orange solid. LC-MS (METHOD B): $R_T = 3.30$ minutes, MS: 229.23

(M+H)⁺.

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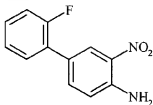
(d) 3-nitrophenyl-4-ylamine



By proceeding in a manner similar to Reference Example 34(a) above but using phenyl boronic acid there was prepared 3-nitrophenyl-4-ylamine as a red solid. LC-MS (METHOD B): $R_T = 3.43$ minutes,

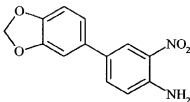
10 215.06 (M+H)⁺.

(e) 2'-fluoro-3-nitro-biphenyl-4-ylamine

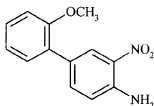


By proceeding in a manner similar to Reference Example 34(a) above but using 2-fluorophenyl boronic acid there was prepared 2'-fluoro-3-nitro-biphenyl-4-ylamine as a red solid. LC-MS (METHOD B):
15 $R_T = 3.33$ minutes, 233.3 (M+H)⁺.

(f) 4'-benzo[1,3]dioxo-5-yl-2-nitrophenylamine

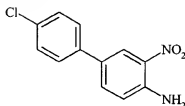


20 By proceeding in a manner similar to Reference Example 34(a) above but using 3,4-methylenedioxyphenyl boronic acid there was prepared 4'-benzo[1,3]dioxo-5-yl-2-nitrophenylamine as an orange solid. LC-MS (METHOD B): $R_T = 3.23$ minutes, 259.3 (M+H)⁺.

(g) 2'-methoxy-3-nitro-biphenyl-4-ylamine

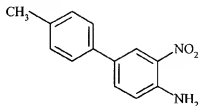
By proceeding in a manner similar to Reference Example 34(a) above but using 2-methoxyphenyl boronic acid there was prepared 2'-methoxy-3-nitro-biphenyl-4-ylamine as an orange solid. LC-MS

5 (METHOD B): $R_T = 3.30$ minutes, $245.3 (M+H)^+$.

(h) 4'-chloro-3-nitro-biphenyl-4-ylamine

By proceeding in a manner similar to Reference Example 34(a) above but using 4-chlorophenyl boronic acid there was prepared 4'-chloro-3-nitro-biphenyl-4-ylamine as an orange solid. LC-MS

10 (METHOD B): $R_T = 3.45$ minutes, $249.27 (M+H)^+$.

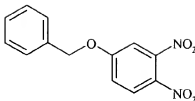
(i) 4'-methyl-3-nitro-biphenyl-4-ylamine

By proceeding in a manner similar to Reference Example 34(a) above but using 4-methylphenyl boronic acid there was prepared 4'-methyl-3-nitro-biphenyl-4-ylamine as an orange solid. LC-MS

15 (METHOD B): $R_T = 3.33$ minutes, $229.2 (M+H)^+$.

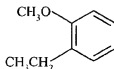
REFERENCE EXAMPLE 35

20 (a) 4-benzyloxy-1,2-dinitrobenzene



- A stirred solution of 3,4-dinitrophenol (1g) in dimethylformamide (30mL) was treated with benzyl bromide (723 μ L) and potassium carbonate (1.13g). The reaction mixture was stirred at ambient temperature for 24 hours and then partitioned between ethyl acetate and water. The organic layer was washed with brine, then dried over magnesium sulfate and then evaporated. The residue was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and hexane (1:4, v/v) to give 4-benzyloxy-1,2-dinitrobenzene (1.30g) as a yellow solid. LC-MS (METHOD B): R_T = 3.31 minutes. ^1H NMR [(CD₃)₂CO, ppm): δ 5.28 (s, 2H), 7.26-7.42 (m, 6H), 7.57 (d, 1H), 8.12 (d, 1H).

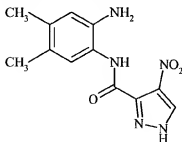
- 10 (b) 1-Ethyl-2-methoxy-benzene



- By proceeding in a manner similar to Reference Example 35(a) above, but using 2-ethylphenol (5ml) and iodomethane (2.6 ml) with acetone as solvent and heating at 70°C for 24 hours in a sealed pressure vessel, there was prepared 1-ethyl-2-methoxy-benzene (5.6 g) as a yellow oil which was used without future purification. LC-MS (METHOD K): R_T = 3.83 minutes. ^1H NMR (d_6 acetone) : δ 6.95 (m, 2H), 6.75 (d, 1H), 6.68 (t, 1H), 3.67 (s, 3H), 2.44 (q, 2H) 0.95 (t, 3H).

REFERENCE EXAMPLE 36

- (a) 4-Nitro-1H-pyrazole-3-carboxylic acid (2-amino-4,5-dimethylphenyl)amide



20

Method A A stirred solution of 4,5-dimethylphenylenediamine (4.32g) and diisopropylethylamine (30ml) in dichloromethane (200ml) was treated with 4-nitropyrazole-3-carboxylic chloride (5g) portionwise at 0°C. The reaction mixture was warmed to ambient temperature and stirred for 30 minutes. The solvent was removed *in vacuo* and the oily residue was partitioned between ethyl acetate

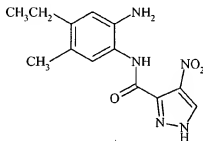
and water. The organic layer was dried over magnesium sulfate and concentrated. The residual oil was re-crystallised from ethyl acetate and methanol (10%) to give 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4,5-dimethylphenyl)amide (6.58g) as an orange solid. LC-MS (METHOD B): $R_T = 2.36$ minutes, 276.09 (M+H)⁺.

5

Method B Polyphosphoric acid (500g) was added to a 1 L flask equipped with an overhead stirrer and heated to 70°C under nitrogen. A blended mixture of 4-nitro-3-pyrazole carboxylic acid (50g) and 1,2-diamino-4,5-dimethylbenzene (43.4g) was added and the mixture was heated to 180°C. After 1 hour at this temperature the reaction mixture was cooled to 130°C and poured into ice water (2.5kg).

- 10 This mixture was stirred with an overhead stirrer and then treated with aqueous ammonium hydroxide (350mL, 30%) until the pH was 2.1. After stirring for a further 15 minutes the mixture was filtered and the filtered solid was washed three times with water (200mL) then dried under vacuum to give 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4,5-dimethylphenyl)amide as a brown solid.

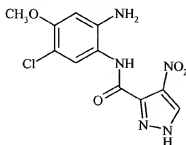
- 15 (b) 4-Nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-ethyl-5-methylphenyl)amide



By proceeding in a manner similar to Reference Example 36(a), Method A, above but using 4-ethyl-5-methyl-phenylene diamine [Reference Example 30(a)] there was prepared 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-ethyl-5-methylphenyl)amide as a dark red solid. LC-MS (METHOD B):

- 20 $R_T = 2.89$ minutes, 290.24 (M+H)⁺.

- (c) 4-Nitro-1H-pyrazole-3-carboxylic acid (2-amino-5-chloro-4-methoxyphenyl)amide

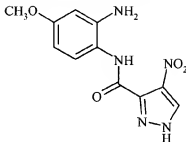


By proceeding in a manner similar to Reference Example 36(a), Method A, above but using 4-chloro-5-methoxybenzene-1,2-diamine [1g, Reference Example 49(b)], diisopropylctylamine (4.1mL, 4 eq),

25

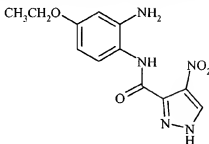
- dichloromethane (50 mL) and a solution of 4-nitropyrazole-3-carbonyl chloride (1g, 5.8 mmol) in dichloromethane (25 mL) and stirring the reaction mixture at ambient temperature for 18 hours there was prepared a mixture of 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-5-chloro-4-methoxyphenyl)amide and the bis-acylated material, MS 310 (M⁺) and 449 (M⁺). This material was used without further purification in Example 20(c).

(d) 4-Nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-methoxy-phenyl)-amide



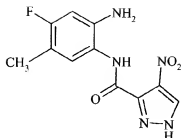
- By proceeding in a manner similar to Reference Example 36(a), Method A, above but using 4-methoxy-1,2-phenylenediamine (880mg) and 4-nitropyrazole-3-carboxylic chloride [prepared by treating a solution of 4-nitropyrazole-3-carboxylic acid (1g) in dry dichloromethane (70ml) under nitrogen with oxalyl chloride (1.1ml) and dimethylformamide and after stirring overnight evaporating the reaction mixture then azeotrope three times with toluene (10ml)] there was prepared 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-methoxy-phenyl)-amide (800mg). LC-MS (Method J): R_T = 2.67 minutes, 278.25 (M+H)⁺, 276.28 (M-H)⁻.

(e) 4-Nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-ethoxy-phenyl)-amide



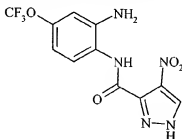
- By proceeding in a manner similar to Reference Example 36(d) above but using 4-ethoxy-benzene-1,2-diamine [1.25g, Reference Example 30(v)] and subjecting the reaction product to flash chromatography on silica, eluting initially with ethyl acetate and then with a mixture of ethyl acetate and methanol (9:1, v/v), there was prepared 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-ethoxy-phenyl)-amide (824mg) a black solid. LC-MS (Method J): R_T = 2.90 minutes, 292.27 (M+H)⁺, 290.30 (M-H)⁻.
- (f) 4-Nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-fluoro-5-methyl-phenyl)-amide

-526-



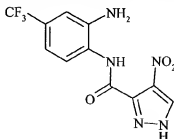
- By proceeding in a manner similar to Reference Example 36(d) above but using 4-fluoro-5-methyl-benzene-1,2-diamine [Reference Example 30(w)] there was prepared 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-fluoro-5-methyl-phenyl)-amide (2.12g) as a red oil. LC-MS (METHOD J): $R_T = 3.02$ minutes, $280.25 (M+H)^+$.

(g) 4-Nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-trifluoromethoxy-phenyl)-amide



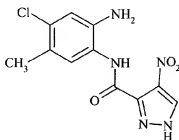
- By proceeding in a manner similar to Reference Example 36(d) above but using 4-trifluoromethoxy-benzene-1,2-diamine [Reference Example 30(x)] there was prepared 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-trifluoromethoxy-phenyl)-amide (0.850g) as a red solid. LC-MS (METHOD J): $R_T = 3.34$ minutes, $332.21 (M+H)^+$.

(h) 4-Nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-trifluoromethyl-phenyl)-amide



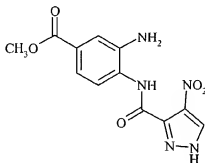
- By proceeding in a manner similar to Reference Example 36(d) above but using 4-trifluoromethyl-benzene-1,2-diamine [Reference Example 30(y)] there was prepared 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-trifluoromethyl-phenyl)-amide (0.250g) as a red solid. LC-MS (METHOD B): $R_T = 3.35$ minutes, $316.14 (M+H)^+$.

- (i) 4-Nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-chloro-5-methyl-phenyl)-amide



- By proceeding in a manner similar to Reference Example 36(d) above but using 4-chloro-5-methyl-benzene-1,2-diamine there was prepared 4-nitro-1H-pyrazole-3-carboxylic acid (2-amino-4-chloro-5-methyl-phenyl)-amide (0.300g) as a yellow solid. LC-MS (METHOD B): $R_T = 2.72$ minutes, 296.10 (M+H)⁺.

- (j) 3-Amino-4-[(4-nitro-1H-pyrazole-3-carbonyl)-amino]-benzoic acid methyl ester



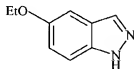
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By proceeding in a manner similar to Reference Example 36(d) above but using methyl-3,4-diaminobenzoate there was prepared 3-amino-4-[(4-nitro-1H-pyrazole-3-carbonyl)-amino]-benzoic acid methyl ester (2.51g) as a tan foam solid. LC-MS (METHOD B): $R_T = 2.83$ minutes, 306.21 (M+H)⁺.

15

REFERENCE EXAMPLE 37

5-Ethoxy-1H-indazole



20

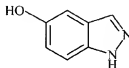
A solution of 5-hydroxy-1H-indazole[0.5g, Reference Example 38] in acetone (10ml) was treated with potassium carbonate (2.56g) then with iodoethane (0.296ml). The mixture was refluxed for 4 hours then cooled and then evaporated. The residue was partitioned between ethyl acetate and water and the aqueous layer was further extracted twice with ethyl acetate. The combined organic fractions were dried over magnesium sulfate and then evaporated to yield a brown residue which was subjected to

flash column chromatography on silica eluting with a mixture of ethyl acetate and hexane (1:1, v/v) to give 5-ethoxy-1H-indazole (0.38g) as an off-white solid. LC-MS (METHOD B): R_T =2.68 minutes; 163 (M+H)⁺.

5

REFERENCE EXAMPLE 38

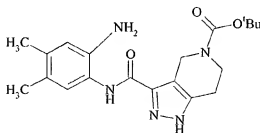
5-Hydroxy-1H-indazole



- A solution of 5-methoxy-1H-indazole [0.410g, Reference Example 24(a)] in dichloromethane (7.5ml) was treated with a solution of boron tribromide in dichloromethane (7.5ml, 1M). The mixture was then heated to reflux for 4 hours, then cooled to 0°C and then treated dropwise with water (2ml). The pH of this mixture was adjusted to 7-8 by addition of 10% aqueous sodium hydrogen carbonate. The mixture was then extracted three times with ethyl acetate. The combined extracts were dried over magnesium sulfate and then evaporated. The residual brown oil was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and hexane (1:1, v/v) to give 5-hydroxy-1H-indazole (0.310g) as a yellow solid. LC-MS (METHOD B): R_T =1.96 minutes; 135 (M+H)⁺.

REFERENCE EXAMPLE 39

- (a) 1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-3,5-dicarboxylic acid, 3-(2-amino-4,5-dimethylphenyl)amide, 5-tert-butyl ester

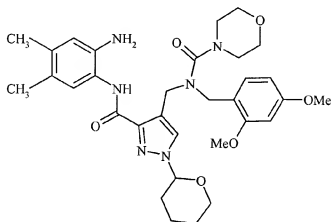


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- To a solution of 4,5-dimethylbenzene-1,2-diamine (0.841g) and 1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-3,5-dicarboxylic acid 5-tert-butyl ester [1.5g, Reference Example 40(a)] in dimethyl formamide (100ml) was added diisopropylethylamine (1.08ml) and 2-(1H-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (2.35g). The mixture was stirred for 1.5 hours and diluted with ethyl acetate then washed six times with brine. The organic layer was dried over magnesium sulfate and concentrated in vacuo to yield a pale brown solid. The solid was then triturated with methanol to yield 1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-3,5-dicarboxylic acid, 3-(2-amino-4,5-dimethylphenyl)amide, 5-tert-butyl ester (0.99g) as an off-white solid.

LC-MS (METHOD B): $R_T = 2.94$ minutes; $386 (M+H)^+$.

- (b) Morpholine-4-carboxylic acid [3-(2-amino-4,5-dimethyl-phenylcarbamoyl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-ylmethyl]-(2,4-dimethoxy-benzyl)-amide

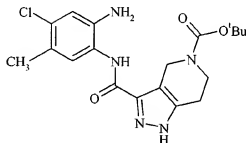


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By proceeding in a manner similar to Reference Example 39(a) above but using 4-[[2,4-dimethoxy-benzyl)-(morpholine-4-carbonyl)-amino]-methyl]-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid [534mg, Reference Example 40(b)] there was prepared morpholine-4-carboxylic acid [3-(2-amino-4,5-dimethyl-phenylcarbamoyl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-ylmethyl]-(2,4-dimethoxy-

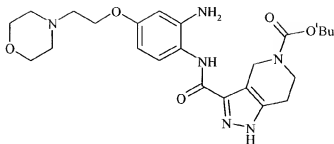
- 10 benzyl)-amide (1.66g) as a yellow oil. LC-MS (METHOD B): $R_T = 2.81$ minutes, $607.71 (M+H)^+$.

- (c) 3-(2-Amino-4-chloro-5-methyl-phenylcarbamoyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester



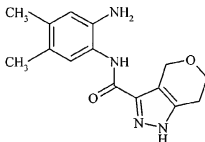
- 15 By proceeding in a manner similar to Reference Example 39(a) above but using 4-chloro-5-methyl-1,2-phenylenediamine there was prepared 3-(2-amino-4-chloro-5-methyl-phenylcarbamoyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (411mg) as a brown solid. LC-MS (METHOD J): $R_T = 3.66$ minutes, $406/408 (M+H)^+$.

- 20 (d) 3-[2-Amino-4-(2-morpholin-4-yl-ethoxy)-phenylcarbamoyl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester



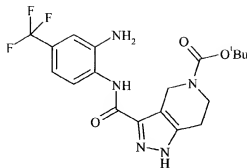
By proceeding in a manner similar to Reference Example 39(a) above but using 4-(2-morpholin-4-yl-ethoxy)-benzene-1,2-diamine [Reference Example 29(c)] there was prepared 3-[2-amino-4-(2-morpholin-4-yl-ethoxy)-phenyl]carbamoyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (400mg) as a brown solid. LC-MS (METHOD N): $R_T = 3.33$ minutes, 485.18 (M-H)⁺.

(e) 1,4,6,7-Tetrahydro-pyran[4,3-c]pyrazole-3-carboxylic acid (2-amino-4,5-dimethyl-phenyl)-amide



By proceeding in a manner similar to Reference Example 39(a) above but using 1,4,6,7-tetrahydro-pyran[4,3-c]pyrazole-3-carboxylic acid [Reference Example 17(e)] there was prepared 1,4,6,7-tetrahydro-pyran[4,3-c]pyrazole-3-carboxylic acid (2-amino-4,5-dimethyl-phenyl)-amide (116mg) as a cream solid. LC-MS (METHOD B): $R_T = 2.32$ minutes, 287 (M+H)⁺.

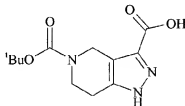
(f) 3-(2-Amino-4-trifluoromethyl-phenyl)carbamoyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester



- By proceeding in a manner similar to Reference Example 39(a) above but using 4-trifluoromethyl-1,2-phenylenediamine there was prepared 3-(2-amino-4-trifluoromethyl-phenylcarbamoyl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester (1.00g) as a brown solid. LC-MS
- 5 (METHOD N): $R_T = 3.75$ minutes, 424.10 (M-H)⁺.

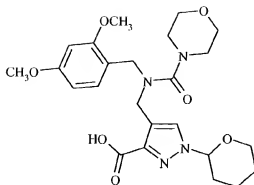
REFERENCE EXAMPLE 40

- (a) 1,4,6,7-Tetrahydro-pyrazolo[4,3-c]pyridine-3,5-dicarboxylic acid 5-tert-butyl ester



- 10 A solution of 1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-3,5-dicarboxylic acid 5-tert-butyl ester 3-ethyl ester [5.105g, Reference Example 18(d)] and lithium hydroxide monohydrate (0.870g) in methanol (30ml) and water (10ml) was stirred at 55°C for 2.5 hours. The mixture was acidified with saturated aqueous potassium hydrogen sulfate solution and extracted three times with ethyl acetate. The organic extracts were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield 1,4,6,7-
- 15 tetrahydro-pyrazolo[4,3-c]pyridine-3,5-dicarboxylic acid 5-tert-butyl ester (4.442g) as a pale yellow solid. MS: 268 (M+H)⁺. HPLC (METHOD G): $R_T = 2.86$ minutes.
- (b) 4-[(2,4-dimethoxy-benzyl)-(morpholine-4-carbonyl)-amino]-methyl-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid

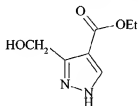
-532-



- By proceeding in a manner similar to Reference Example 40(a) above but using 4-(((2,4-dimethoxybenzyl)-(morpholine-4-carbonyl)-amino)-methyl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid ethyl ester [594mg, Reference Example 48(i)] there was prepared 4-(((2,4-dimethoxybenzyl)-(morpholine-4-carbonyl)-amino)-methyl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid (534mg) as a white fluffy solid. LC-MS (Method B): $R_T = 2.71$ minutes, 489.21 (M+H)⁺.

REFERENCE EXAMPLE 41

- (a) 3-Hydroxymethyl-1H-pyrazole-4-carboxylic acid ethyl ester

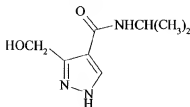


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- A solution of 3-*tert*-butoxymethyl-1H-pyrazole-4-carboxylic acid ethyl ester [3.46g, Reference Example 42] in dichloromethane (25ml) was treated with trifluoroacetic acid (25ml). The mixture was stirred for 1.5 hours and then concentrated. The residue was partitioned between saturated sodium carbonate solution and ethyl acetate. The organic layer was dried over magnesium sulfate and then evaporated to give 3-hydroxymethyl-1H-pyrazole-4-carboxylic acid ethyl ester (2.49g) as a brown solid which was used without further purification. LC-MS (METHOD B): $R_T = 2.54$ minutes; 171 (M+H)⁺.

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- (b) 3-Hydroxymethyl-1H-pyrazole-4-carboxylic acid isopropylamide

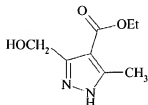


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- By proceeding in a manner similar to Reference Example 41(a) above but using 3-*tert*-butoxymethyl-1H-pyrazole-4-carboxylic acid isopropylamide [Reference Example 44(a)] there was prepared

3-hydroxymethyl-1H-pyrazole-4-carboxylic acid isopropylamide as a pale yellow solid, which was used without further purification. LC-MS (METHOD B): $R_T = 2.43$ minutes; 184 (M+H)⁺.

(c) 3-Hydroxymethyl-5-methyl-1H-pyrazole-4-carboxylic acid ethyl ester

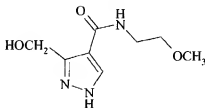


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By proceeding in a manner similar to Reference Example 41(a) above but using 3-*tert*-butoxymethyl-5-methyl-1H-pyrazole-4-carboxylic acid ethyl ester [Reference Example 43] there was prepared 3-hydroxymethyl-5-methyl-1H-pyrazole-4-carboxylic acid ethyl ester as a orange solid which was used without further purification. LC-MS (METHOD B): $R_T = 2.58$ minutes; 185 (M+H)⁺.

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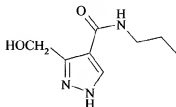
(d) 3-Hydroxymethyl-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide



By proceeding in a manner similar to Reference Example 41(a) above but using 3-*tert*-butoxymethyl-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide [Reference Example 44(b)] there was prepared 3-hydroxymethyl-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide (398mg) as an orange oil. LC-MS (METHOD B): $R_T = 1.66$ minutes, 222 (M+Na)⁺.

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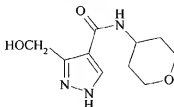
(e) 3-Hydroxymethyl-1H-pyrazole-4-carboxylic acid propylamide



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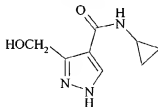
By proceeding in a manner similar to Reference Example 41(a) above but using 3-*tert*-butoxymethyl-1H-pyrazole-4-carboxylic acid propylamide [Reference Example 44(c)] there was prepared 3-hydroxymethyl-1H-pyrazole-4-carboxylic acid propylamide (731mg) as an orange oil. LC-MS (METHOD B): $R_T = 2.09$ minutes, 206 (M+Na)⁺.

- (f) 3-Hydroxymethyl-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide



- By proceeding in a manner similar to Reference Example 41(a) above but using 3-*tert*-butoxymethyl-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-lamide [Reference Example 44(d)] there was prepared 3-hydroxymethyl-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide (4.10g) as an orange oil. LC-MS (METHOD N): $R_T = 1.89$ minutes, $226(M+H)^+$.

- (g) 3-Hydroxymethyl-1H-pyrazole-4-carboxylic acid cyclopropylamide

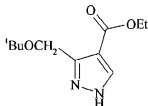


- By proceeding in a manner similar to Reference Example 41(a) above but using 3-*tert*-butoxymethyl-1H-pyrazole-4-carboxylic acid cyclopropylamide [Reference Example 44(e)] there was prepared 3-hydroxymethyl-1H-pyrazole-4-carboxylic acid cyclopropylamide (2.48g) as a white foam. LC-MS (METHOD N): $R_T = 1.85$ minutes, $180.15 (M+H)^+$.

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REFERENCE EXAMPLE 42

3-*tert*-Butoxymethyl-1H-pyrazole-4-carboxylic acid ethyl ester



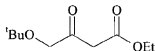
- A solution of dimethyl formamide acetal (3.47ml) and 4-*tert*-butoxy-3-oxo-butyric acid ethyl ester [3.52g, Reference Example 43] in toluene (50ml) was heated at 65°C for 2 hours. The mixture was then concentrated and the residue redissolved in acetic acid (3ml). To the mixture was added hydrazine hydrate (0.93ml) and the whole allowed to stir at ambient temperature for 2 hours. The mixture was again concentrated *in vacuo* and the residue partitioned between ethyl acetate and 5% aqueous sodium hydrogen carbonate solution. The organic layer was dried over magnesium sulfate and

then concentrated to yield a brown oil which was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and petrol (3:7, v/v) to give 3-tert-butyloxymethyl-1H-pyrazole-4-carboxylic acid ethyl ester (3.46g) as a yellow solid. LC-MS (METHOD B): R_T = 2.79 minutes; 227 (M+H)⁺.

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REFERENCE EXAMPLE 43

4-tert-Butoxy-3-oxo-butyric acid ethyl ester

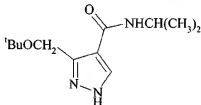


- A suspension of sodium hydride (4.44g, 60% dispersion in mineral oil) in dimethyl formamide (50ml), at 0°C, was treated dropwise with ethyl 4-chloroacetoacetate (5ml) and then with *tert*-butyl alcohol (7.08ml). This mixture was maintained at 0°C for 2 hours, then a further 2 hours at ambient temperature and then poured onto 2N hydrochloric acid/ice and then extracted four times with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate solution, then with water, then with brine, then dried over magnesium sulfate and then evaporated. The resulting yellow oil was subjected to flash column chromatography on silica eluting with a mixture of ethyl acetate and petrol (1:9, v/v) to give 4-tert-butoxy-3-oxo-butyric acid ethyl ester (5.20g) as a yellow oil. TLC (silica, 1:4, v/v ethyl acetate/petrol): R_F = 0.51. NMR (400MHz, CDCl₃): δ 1.21(9H, s), 1.28(3H, t), 3.55(2H, s), 4.19(2H, q).

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REFERENCE EXAMPLE 44

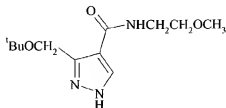
- (a) 3-tert-Butyloxymethyl-1H-pyrazole-4-carboxylic acid isopropylamide



- To a solution of 3-*tert*-butyloxymethyl-1H-pyrazole-4-carboxylic acid [1.520g, Reference Example 17(d)], hydroxybenzotriazole (3.110g) and diisopropyl ethylamine (4.010ml) in dimethyl formamide (130ml) was added isopropylamine (1.960ml) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.420g). The mixture was heated at 70°C for 2.5 hours, then diluted with ethyl acetate, then washed with water, then with brine, then dried over magnesium sulfate and then evaporated. The residue was triturated with a mixture of ethyl acetate and petrol to yield 3-tert-butyloxymethyl-1H-pyrazole-4-carboxylic acid isopropylamide (652mg) as an off-white solid.
- LC-MS (METHOD B): 2.99 minutes; 240 (M+H)⁺.

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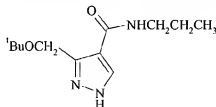
- (b) 3-tert-Butyloxymethyl-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide



By proceeding in a manner similar to Reference Example 44(a) above but using 2-methoxyethylamine,

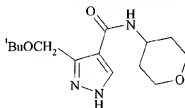
- 5 there was prepared 3-tert-butyloxymethyl-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide (811mg) as an orange oil. LC-MS (METHOD B): $R_T = 2.43$ minutes, 278 (M+Na)⁺.

- (c) 3-tert-Butyloxymethyl-1H-pyrazole-4-carboxylic acid propylamide



- 10 By proceeding in a manner similar to Reference Example 44(a) above but using n-propylamine there was prepared 3-tert-butyloxymethyl-1H-pyrazole-4-carboxylic acid propylamide (1.12g) as an orange oil. LC-MS (METHOD B): $R_T = 2.65$ minutes, 262 (M+Na)⁺.

- (d) 3-tert-Butyloxymethyl-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-lamide

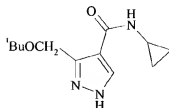


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By proceeding in a manner similar to Reference Example 44(a) above but using tetrahydropyran-4-ylamine there was prepared 3-tert-butyloxymethyl-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-lamide (5.50g) as an orange oil. LC-MS (METHOD N): $R_T = 3.05$ minutes, 282 (M+H)⁺.

- 20 (e) 3-tert-Butyloxymethyl-1H-pyrazole-4-carboxylic acid cyclopropylamide

-537-

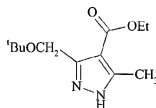


By proceeding in a manner similar to Reference Example 44(a) above but using cyclopropylamine there was prepared 3-tert-butylloxymethyl-1H-pyrazole-4-carboxylic acid cyclopropylamide (3.27g) as an orange oil. LC-MS (METHOD H): $R_T = 2.24$ minutes, 238.38 (M+H)⁺.

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REFERENCE EXAMPLE 45

3-tert-Butyloxymethyl-5-methyl-1H-pyrazole-4-carboxylic acid ethyl ester

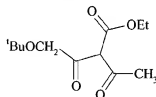


- To a solution of 2-acetyl-4-tert-butoxy-3-oxo-butyric acid ethyl ester [0.325g, Reference Example 46] in acetic acid (3ml) was added hydrazine hydrate (71μL). The mixture was stirred at ambient temperature for 16 hours and then evaporated to remove the acetic acid. The residue was dissolved in ethyl acetate and the solution was washed with 5% sodium hydrogen carbonate solution, then with water, then dried over magnesium sulfate, and then evaporated to yield 3-tert-butylloxymethyl-5-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (0.258g) as a yellow oil which was used without further purification. LC-MS (METHOD B): $R_T = 3.22$ minutes; 241 (M+H)⁺.

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REFERENCE EXAMPLE 46

2-Acetyl-4-tert-butoxy-3-oxo-butyric acid ethyl ester

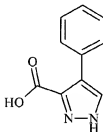


- A suspension of dry magnesium chloride (0.471g) in dichloromethane (6ml) was treated with 4-tert-butoxy-3-oxo-butyric acid ethyl ester [1.00g, Reference Example 43]. This mixture was cooled to 0°C, then treated with pyridine (0.80ml), then stirred for 15 minutes at 0°C and then treated with acetyl chloride (0.352ml). After stirring for a further 15 minutes at 0°C and then for 1 hour at ambient temperature the reaction mixture was treated with saturated aqueous ammonium chloride solution and

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then extracted twice with ethyl acetate. The combined extracts were dried over magnesium sulfate and then evaporated to yield 2-acetyl-4-*tert*-butoxy-3-oxo-butyric acid ethyl ester (1.15g) as a yellow oil which was used without further purification. LC-MS (METHOD B): $R_T = 3.16$ minutes; 243 (M-H)⁺.

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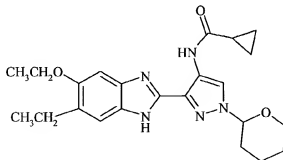
REFERENCE EXAMPLE 474-Phenyl-1H-pyrazole-3-carboxylic acid

- A solution of 3-methyl-4-phenylpyrazole (1.00g) in *tert*-butanol (15ml) and water (25ml), at 60°C, was treated portionwise potassium permanganate (5.47g). The temperature was then slowly elevated to 90°C and maintained at that temperature for 5 hours. The mixture was then cooled and filtered through a pad of celite. The filtrate was concentrated and the pH was adjusted to 10 to 14 by addition of 5N aqueous sodium hydroxide solution. This mixture was washed twice with ethyl acetate. The aqueous layer was then acidified to pH 3 to 5 and then extracted four times with ethyl acetate. The combined extracts were dried over magnesium sulfate and then evaporated to yield 4-phenyl-1H-pyrazole-3-carboxylic acid (0.512g) as a white solid, which was used without further purification. MS:189 (M+H)⁺. HPLC (METHOD B): $R_T = 2.48$ minutes.

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REFERENCE EXAMPLE 48

- (a) Cyclopropanecarboxylic acid [3-(5-ethoxy-6-ethyl-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide

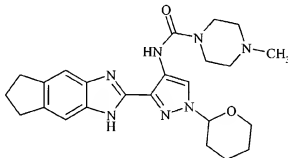


A solution of 3-(5-ethoxy-6-ethyl-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-ylamine [0.3 g, Reference Example 49(a)] and triethylamine (0.8 mL, excess) in tetrahydrofuran (20mL) was treated dropwise with cyclopropanecarbonyl chloride (0.3 g, 2.4 mmol). This mixture was

stirred for 48 hours then diluted with aqueous sodium bicarbonate solution (100 mL) and then extracted twice with ethyl acetate (100mL). The combined extracts were evaporated and the residue was dissolved in tetrahydrofuran (50mL). This solution was treated with a solution of potassium hydroxide (1.1 g) in ethanol (10 mL) and the mixture was stirred for 2 hours, then poured into water (100 mL) and then extracted twice with ethyl acetate (100mL). The combined extracts were evaporated and the residue was chromatographed on silica gel eluting with a mixture of heptane and ethyl acetate (1/1, v/v) to give cyclopropanecarboxylic acid [3-(5-ethoxy-6-ethyl-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide (0.3g) as an off-white solid. LC-MS (Method E): R_T = 2.99 minutes, 424 (M+H)⁺.

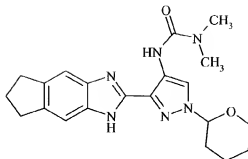
10

- (b) 4-Methylpiperazine-1-carboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide



- By proceeding in a similar manner to Reference Example 48(a) above but (i) treating a solution of 3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-ylamine [302mg, Reference Example 49(d)] and triethylamine (0.94g, 10 eq) in tetrahydrofuran (10 mL) with 4-methylpiperazine-1-carbonyl chloride (930mg, 4.67 mmol), (ii) stirring the mixture at 45°C for 4 hours, then at 55°C for 1 hour, (iii) treating the cooled reaction mixture with aqueous sodium bicarbonate (200mL) and extracting this mixture three times with ethyl acetate (100mL), and (iv) evaporating the combined extracts and chromatographing the residue on silica gel (ethyl acetate/gradient 5-20% methanol) there was prepared 4-methylpiperazine-1-carboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide (189mg) as a purple solid. LC-MS (Method F): R_T = 2.28 minutes, 450 (M+H)⁺.
- (c) 1,1-Dimethyl-3-[3-(1,5,6,7-tetrahydro-s-indacen-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]urea

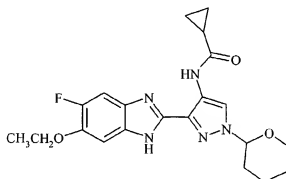
-540-



By proceeding in a similar manner to Reference Example 48(b) above but using dimethylcarbamy chloride (4 eq) there was prepared 1,1-dimethyl-3-[3-(1,5,6,7-tetrahydro-s-indacen-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]urea as a beige foam. LC-MS (Method F): $R_T = 3.22$ minutes,

5 $395 (M+H)^+$.

(d) Cyclopropanecarboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide

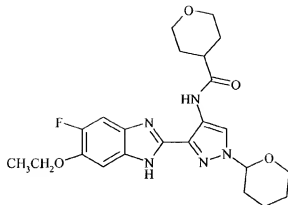


10 By proceeding in a similar manner to Reference Example 48(a) above but using 6-ethoxy-5-fluoro-2[4-amino-1-(tetrahydropyran-2-yl)-1H-pyrazole-3-yl]-1H-benzimidazole [0.45g, Reference Example 49(e)] and subjecting the reaction product to chromatography on silica gel (heptane/ethyl acetate, 7/3,v/v) there was prepared cyclopropanecarboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide (90mg). LC-MS (Method G): $R_T = 8.1$ minutes, 414

15 $(M+H)^+$.

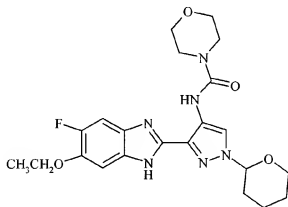
(e) Tetrahydropyran-4-carboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazole-4-yl]amide

-541-



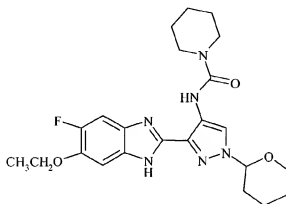
- By proceeding in a similar manner to Reference Example 48(a) above but using 6-ethoxy-5-fluoro-2[4-amino-1-(tetrahydropyran-2-yl)-1H-pyrazole-3-yl]-1H-benzimidazole [0.45g, Reference Example 49(e)] and tetrahydropyran-4-carbonyl chloride (0.135g) and subjecting the reaction product to chromatography on silica gel (heptane/ethyl acetate, 7/3, v/v) there was prepared tetrahydropyran-4-carboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide (120mg). LC-MS (Method G): $R_T = 8.05$ minutes, 458 (M+H)⁺.

- (f) Morpholine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide



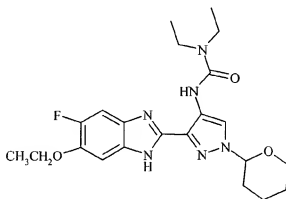
- By proceeding in a similar manner to Reference Example 48(a) above but (i) treating 6-ethoxy-5-fluoro-2[4-amino-1-(tetrahydropyran-2-yl)-1H-pyrazole-3-yl]-1H-benzimidazole [90mg, Reference Example 49(e)] and diisopropylethylamine (168mg) in tetrahydrofuran (4 mL) with morpholine-4-carbonyl chloride (194mg) for 2 days at ambient temperature, and (ii) subjecting the reaction product to chromatography on silica gel (heptane/ethyl acetate, 2/1, v/v), there was prepared morpholine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide (140 mg). LC-MS (Method G): $R_T = 7.85$ minutes, 459 (M+H)⁺.

- (g) Piperidine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide



- By proceeding in a similar manner to Reference Example 48(f) above but using piperidine-1-carbonyl chloride (191mg) there was prepared piperidine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]amide (127mg). LC-MS (Method G): $R_T = 8.2$ minutes, 457 (M+H)⁺.

- (h) 3-[6-Ethoxy-5-fluoro-1H-benzimidazol-2-yl]-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]-1,1-diethylurea

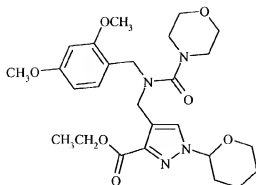


- By proceeding in a similar manner to Reference Example 48(f) above but using diethylcarbonyl chloride (175mg) there was prepared 3-[6-ethoxy-5-fluoro-1H-benzimidazol-2-yl]-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-yl]-1,1-diethylurea (110mg). LC-MS (Method G) $R_T = 7.9$ minutes, 445 (M+H)⁺.

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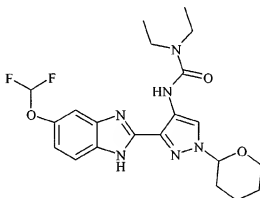
- (i) 4-[[2,4-Dimethoxy-benzyl)-(morpholine-4-carbonyl)-amino]-methyl]-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid

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By proceeding in a similar manner to Reference Example 48(a) above but (i) using 4-[(2,4-dimethoxy-benzylamino]-methyl]-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid ethyl ester (829mg, Reference Example 60) and 4-morpholinecarbonyl chloride (0.96ml), and (ii) subjecting the reaction product to flash chromatography on silica eluting with ethyl acetate, there was prepared 4-[(2,4-dimethoxy-benzyl)-((morpholine-4-carbonyl)-amino)-methyl]-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid (595mg) as a colourless oil. LC-MS (Method B): $R_T = 2.96$ minutes, 517.30 (M+H)⁺.

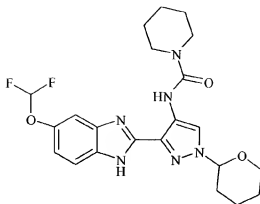
(j) 3-[3-(5-Difluoromethoxy-1H-benzoimidazol-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea



By proceeding in a manner similar to Reference Example 48(a) above but using 3-(5-difluoromethoxy-1H-benzoimidazol-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-ylamine [Reference Example 49(g)] and diethylcarbonyl chloride, there was prepared 3-[3-(5-difluoromethoxy-1H-benzoimidazol-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea (220mg) as a pale brown solid. LC-MS (METHOD K): $R_T = 4.02$ minutes, 447.27 (M-H)⁻.

(k) Piperidine-1-carboxylic acid [3-(5-difluoromethoxy-1H-benzoimidazol-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-yl]-amide

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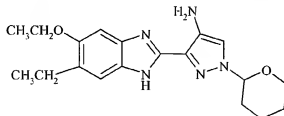


By proceeding in a manner similar to Reference Example 48(j) above but using piperidine-1-carbonyl chloride there was prepared piperidine-1-carboxylic acid [3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-yl]-amide (220mg) as a pale brown solid. LC-MS

5 (METHOD N): $R_T = 4.07$ minutes, 459.28 (M-H)⁺.

REFERENCE EXAMPLE 49

(a) 3-(5-Ethoxy-6-ethyl-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-ylamine

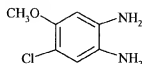


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A solution of 5-ethoxy-6-ethyl-2-[4-nitro-1-(tetrahydropyran-2-yl)-1H-pyrazol-3-yl]-1H-benzimidazole [0.8g, Reference Example 50(a)] in ethanol (100mL) was treated with palladium on carbon (0.1g, 10%) and mixture was hydrogenated at atmospheric pressure (balloon) for 4 days. The catalyst was filtered off, the filtrate was evaporated and the residue was chromatographed on silica gel (ethyl acetate with gradient of 0-10% methanol) to give 3-(5-ethoxy-6-ethyl-1H-benzimidazol-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-ylamine (0.3g) as a solid. LC-MS (Method E): $R_T = 2.15$ minutes, 356 (M+H)⁺.

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(b) 4-chloro-5-methoxybenzene-1,2-diamine

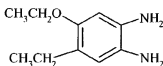


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By proceeding in a similar manner to Reference Example 49 (a) above, but using 5-chloro-4-methoxy-2-nitrophenylamine [Reference Example 31(h)] and subjecting the reaction product to chromatography on silica gel (ethyl acetate with gradient of 40% to 0% heptane) there was prepared 4-chloro-5-methoxybenzene-1,2-diamine (1.0 g) as an orange solid. MS: 173 (M+H)⁺.

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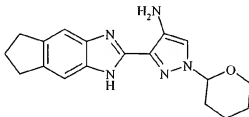
(c) 4-ethoxy-5-ethyl-benzene-1,2-diamine



By proceeding in a similar manner to Reference Example 49(a) above, but using 4-ethoxy-5-ethyl-2-nitrophenylamine [Reference Example 31(g)] and subjecting the reaction product to chromatography on silica gel eluting with ethyl acetate there was prepared 4-ethoxy-5-ethyl-benzene-1,2-diamine as a dark solid. LC-MS (Method E): R_T = 8.434 minutes, 180 (M+H)⁺.

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(d) 3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-ylamine



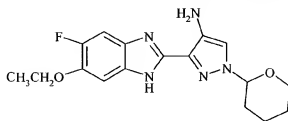
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By proceeding in a similar manner to Reference Example 49(a) above, but (i) using a solution of 2-[4-nitro-1-(tetrahydropyran-2-yl)-1H-pyrazol-3-yl]-1,5,6,7-tetrahydro-1,3-diaza-s-indacene [4.1g, Reference Example 50(b)] in ethanol (120 mL) and 5% palladium on carbon (320 mg), and (ii) using a Parr hydrogenation apparatus at 60 psi for 18 hours there was prepared 3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1-(tetrahydropyran-2-yl)-1H-pyrazol-4-ylamine (368 mg) as a brown solid. LC (Method

20

G): R_T = 3.079 minutes, 324 (M+H)⁺ and 346 (M+Na)⁺.

(e) 6-Ethoxy-5-fluoro-2-[4-amino-1-(tetrahydropyran-2-yl)-1H-pyrazole-3-yl]-1H-benzimidazole

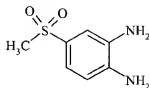


By proceeding in a similar manner to Reference Example 49(a) above, but using 6-ethoxy-5-fluoro-2-[4-nitro-1-(tetrahydropyran-2-yl)-1H-benzimidazole [1.2g, Reference Example 50(c)] there was

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prepared 6-ethoxy-5-fluoro-2-[4-amino-1-(tetrahydropyran-2-yl)-1H-pyrazole-3-yl]-1H-benzimidazole (1.2g). LC-MS (Method G): R_T = 6.74 minutes, 346 (M+H)⁺.

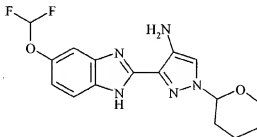
(f) 4-Methanesulfonyl-benzene-1,2-diamine



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By proceeding in a similar manner to Reference Example 49(a) above, but using N*-benzyl-4-methanesulfonyl-benzene-1,2-diamine [Reference Example 65] there was prepared 4-methanesulfonyl-benzene-1,2-diamine as a white solid. LC-MS (METHOD J): R_T = 0.98 minutes, 187.32 (M+H)⁺.

10 (g) 3-(5-Difluoromethoxy-1H-benzoimidazol-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-ylamine

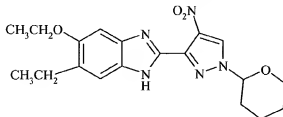


By proceeding in a manner similar to Reference Example 49(a) above but using 5-difluoromethoxy-2-[4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-1H-benzoimidazole [Reference Example 50(e)], there was prepared 3-(5-difluoromethoxy-1H-benzoimidazol-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-ylamine (730mg) as a pale brown solid. LC-MS (METHOD N): R_T = 3.27 minutes, 350.29 (M+H)⁺.

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REFERENCE EXAMPLE 50

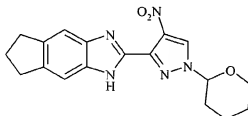
(a) 5-Ethoxy-6-ethyl-2-[4-nitro-1-(tetrahydropyran-2-yl)-1H-pyrazol-3-yl]-1H-benzoimidazole



A mixture of 4-ethoxy-5-ethyl-benzene-1,2-diamine [0.18g, Reference Example 30(s)], 4-nitro-1-

- (tetrahydro-pyran-2-yl)-1H-pyrazole-3-carbaldehyde [0.225g, Reference Example 6(m)] and sodium bisulfite (0.12 g, 1.2 mmol) in dimethylformamide (10mL) was heated at 120°C for 1 hour. The mixture was cooled, water (100 mL) was added and the aqueous mixture was extracted with twice ethyl acetate (50mL). The combined extracts were evaporated and the residue was chromatographed on silica gel (ethyl acetate with gradient of 20-0% heptane) to give 5-ethoxy-6-ethyl-2-[4-nitro-1-(tetrahydropyran-2-yl)-1H-pyrazol-3-yl]-1H-benzimidazole (200mg) as a solid. LC-MS (Method F) $R_T = 2.85$ minutes, 386 (M+H)⁺.

- (b) 2-[4-nitro-1-(tetrahydropyran-2-yl)-1H-pyrazol-3-yl]-1,5,6,7-tetrahydro-1,3-diaza-s-indacene

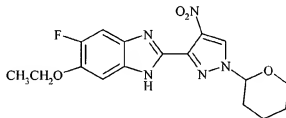


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- By proceeding in a similar manner to Reference Example 50(a) but using indane-5,6-diamine (1.05g, prepared as described by Sui Xiong Cai et al., J.Med.Chem., 1997, 40, pages 730-738) and 4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carbaldehyde [2.5g, Reference Example 6(m)] there was prepared 2-[4-nitro-1-(tetrahydropyran-2-yl)-1H-pyrazol-3-yl]-1,5,6,7-tetrahydro-1,3-diaza-s-indacene which was used without further purification.

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- (c) 6-Ethoxy-5-fluoro-2-[4-nitro-1-(tetrahydropyran-2-yl)-1H-benzimidazole

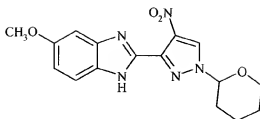


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- By proceeding in a similar manner to Reference Example 50(a) but using 4-ethoxy-5-fluoro-benzene-1,2-diamine (2.2 g, prepared according to the method of Uchida, et al, Chem. Pharm. Bull. 1989, volume 37, pages 1517 to 1523) there was prepared 6-ethoxy-5-fluoro-2-[4-nitro-1-(tetrahydropyran-2-yl)-1H-benzimidazole. LC-MS (Method G): $R_T = 8.1$ minutes, 376 (M+H)⁺.

- (d) 5-Methoxy-2-[4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-1H-benzimidazole

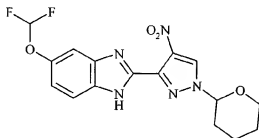
-548-



By proceeding in a similar manner to Reference Example 50(a) but using 4-methoxy-1,2-phenylenediamine (117mg) there was prepared 5-methoxy-2-[4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-1H-benzimidazole (282mg) as a deep red oil. LC-MS (Method H): $R_T = 2.02$ minutes,

5 344.21 (M+H)⁺, 342.24 (M-H)⁻.

(e) 5-Difluoromethoxy-2-[4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-1H-benzimidazole



By proceeding in a manner similar to Reference Example 50(a) above but using difluoromethoxy-benzene-1,2-diamine [Reference Example 30(y)] and 4-nitro-1-(tetrahydropyran-2-yl)-1H-pyrazole-3-carbaldehyde [Reference Example 6(m)], there was prepared 5-difluoromethoxy-2-[4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-1H-benzimidazole (910mg) as a pale brown solid. LC-MS (METHOD N): $R_T = 3.40$ minutes, 380.22 (M+H)⁺.

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REFERENCE EXAMPLE 51

1-Ethoxy-2-ethyl benzene

To a solution of 2-ethylphenol (6.9g, 56.5 mmol), triphenylphosphine (15.7 g, 60 mmol) and ethanol (6 mL, excess) in tetrahydrofuran (100mL) was added dropwise DIAD (12.1g, 60 mmol). After stirring for 18 hours, mixture was evaporated and the residue was chromatographed on silica gel (heptane/ethyl acetate 9/1) to give 1-ethoxy-2-ethyl benzene (7.2g) as a clear liquid. GC-MS shows one peak, $R_T =$

20 5.6 minutes. MS 150 (M+).

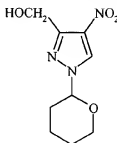
REFERENCE EXAMPLE 52

N-(3-Chloro-4-methoxyphenyl)acetamide

- A solution of 3-chloro-4-methoxyphenylamine (6.3g) and triethylamine (4.04g) in dichloromethane (100 mL) was chilled in an ice bath, acetyl chloride (3.45g) was added dropwise and the mixture was stirred at ambient temperature overnight. The reaction mixture was extracted with water (2X30 mL) and brine (2X30 mL) and the organic layer was dried with magnesium sulfate. The drying agent was removed by filtration and the filtrate was evaporated to give N-(3-chloro-4-methoxyphenyl)acetamide (7.45g) as a dark oil, which solidified on standing. MS: 200 (M+H)⁺.

REFERENCE EXAMPLE 53

[4-Nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-methanol



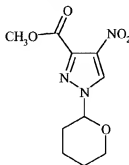
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- A stirred solution of 4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid methyl ester [500mg, Reference Example 54(a)] in tetrahydrofuran (20ml) under nitrogen at -78°C was treated dropwise with a solution of diisobutylaluminum hydride in tetrahydrofuran (8.82ml, 1M). The reaction mixture was stirred at room temperature for 1.5 hours. The reaction mixture was taken up in diethyl ether (100ml) and quenched with water (150ml). The resulting suspension was filtered through celite and the organic layer was collected from the filtrate, then dried over magnesium sulfate and then evaporated to yield [4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-3-yl]-methanol (349mg) as a peach oil. LC-MS (Method H): R_T = 2.08 minutes, 250.29 (M+H+Na)⁺.

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REFERENCE EXAMPLE 54

- (a) 4-Nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid methyl ester

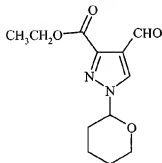


A suspension of 4-nitro-1H-pyrazole-3-carboxylic acid methyl ester (1.3g, Reference Example 55) and p-toluene sulfonic acid (144mg) in chloroform (30ml) at 0°C was treated with 3,4-dihydropyran

-550-

- (1.04ml) dropwise. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate (40ml) and water (3 x 40ml). The combined aqueous layers were extracted with dichloromethane (3 x 60ml). The organic layers were combined, dried over magnesium sulfate and concentrated to yield 4-nitro-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid methyl ester (2.23g) as a viscous brown oil. LC-MS (Method H): $R_T = 2.79$ minutes, 278.21 (M+H+Na)⁺.

- (b) 4-Formyl-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid ethyl ester

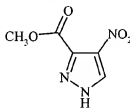


- 10 By proceeding in a manner similar to Reference Example 54(a) above but using 4-formyl-1H-pyrazole-3-carboxylic acid ethyl ester (100mg, Reference Example 57) there was prepared 4-formyl-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid ethyl ester (170mg) was prepared as a viscous yellow oil. LC-MS (Method J): $R_T = 3.29$ minutes, 275.30 (M+H+Na)⁺.

15

REFERENCE EXAMPLE 55

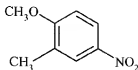
4-Nitro-1H-pyrazole-3-carboxylic acid methyl ester



- A stirred suspension of 4-nitro-3-pyrazolecarboxylic acid (1g) in dichloromethane under nitrogen at 0°C was treated with oxalyl chloride (1.11ml) followed by dimethylformamide (5drops). The reaction mixture was warmed to room temperature and stirred overnight. Methanol (10ml) was added and the reaction mixture was stirred overnight. The solvent was removed under reduced pressure and azeotroped with toluene twice to yield 4-nitro-1H-pyrazole-3-carboxylic acid methyl ester (1.3g) as a pale green solid. LC-MS (Method H): $R_T = 1.94$ minutes, 170.23 (M-H)⁻.

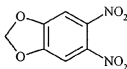
25

REFERENCE EXAMPLE 56

(a) 1-Methoxy-2-methyl-4-nitrobenzene

2-Methylanisole (2.5ml) in acetic acid (140ml) and dichloromethane (150ml) was cooled to 15°C. Concentrated nitric acid (20ml) was added slowly keeping the temperature of the reaction below 40°C.

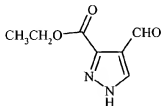
- 5 The reaction was stirred at ambient temperature for 30 minutes and cooled to 0°C before adding fuming nitric acid (50ml) dropwise. The reaction mixture was allowed to warm to ambient temperature slowly and stirred for a further 4 days. The reaction mixture was poured onto ice water (600ml) and the organic layer was washed with water (2 x 40ml) and saturated sodium hydrogencarbonate (2 x 40ml), dried over magnesium sulfate and concentrated. The residual deep red solid was subjected to flash
- 10 silica chromatography on silica eluting with isohexane/ethyl acetate (9:1) to (7:3) to yield 1-methoxy-2-methyl-4-nitrobenzene (2.70g) as an off white solid. LC-MS (Method J): $R_T = 3.74$ minutes, 168.27 (M+H)⁺.

(b) 5,6-Dinitro-benzof[1,3]dioxole

15

By proceeding in a manner similar to Reference Example 56(a) above but using 1,2-methylenedioxybenzene there was prepared 5,6-dinitro-benzof[1,3]dioxole as an orange solid. HPLC (Method C): $R_T = 2.99$ minutes; 490.24 (2M+1).

20

REFERENCE EXAMPLE 574-Formyl-1H-pyrazole-3-carboxylic acid ethyl ester

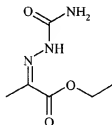
- Phosphorus oxychloride (5.07ml) was added dropwise to dimethylformamide (8.4ml) at 0°C under nitrogen. Ethyl pyruvate semicarbazide (4.3g, Reference Example 58) was added portionwise to the stirring solution at 0°C under a nitrogen positive pressure. The reaction mixture was heated at 60°C for
- 25 2.5 hours and cooled to ambient temperature before pouring slowly onto ice (30g). The pH of the reaction mixture was adjusted to pH12 with 6.25M sodium hydroxide solution whilst maintaining the

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temperature at 0°C. The aqueous reaction mixture was heated at 60°C for 5 minutes and cooled to 0°C. The pH was re-adjusted to pH6 with 1M hydrochloric acid. The resulting precipitate which formed after 1 hour was collected by filtration to yield 4-formyl-1H-pyrazole-3-carboxylic acid ethyl ester (1.02g) as a pale yellow solid. LC-MS (Method J): R_T = 2.55 minutes, 169.27 (M+H)⁺, 167.30 (M-H)⁻.

REFERENCE EXAMPLE 58

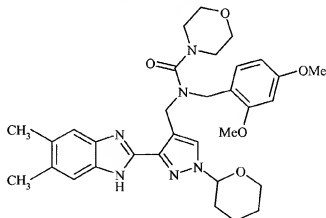
Ethyl pyruvate semicarbazide



- 10 A stirred solution of semicarbazide hydrochloride (11.1g) and sodium acetate (8.2g) in water (250ml) was treated with ethyl pyruvate (10.9ml) in one portion. The resulting white precipitate was collected by filtration to yield ethyl pyruvate semicarbazide (16.59g) as a white powder. LC-MS (Method J): R_T = 2.38 minutes, 174.31 (M+H)⁺, 172.32 (M-H)⁻.

15 REFERENCE EXAMPLE 59

Morpholine-4-carboxylic acid (2,4-dimethoxy-benzyl)-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-ylmethyl]-amide

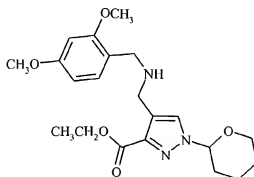


- 20 A stirred solution of [332mg, Reference Example 39(b)] in acetic acid (5ml) was heated at 120°C for 5 minutes in a Personal Chemistry Smith Creator microwave. The mixtures from five reactions were combined and the solvent removed *in vacuo* to yield morpholine-4-carboxylic acid (2,4-dimethoxy-

benzyl)-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-ylmethyl]-amide (1.22g) as a dark yellow oil. LC-MS (Method J): $R_T = 2.70$ minutes, 589.63 (M+H)⁺.

REFERENCE EXAMPLE 60

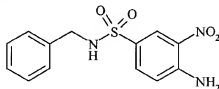
- 5 4-[[[2,4-Dimethoxy-benzyl)-(morpholine-4-carbonyl)-amino]-methyl]-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid ethyl ester



- A stirred solution of 4-[[[2,4-dimethoxy-benzylamino)-methyl]-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid ethyl ester [1g, Reference Example 54(b)] in tetrahydrofuran (25ml) was treated with
 10 2,4-dimethoxybenzylamine (0.596ml). After stirring for 12 hours sodium triacetoxyborohydride (1.68g) was added to the reaction mixture and the reaction mixture was stirred for a further 1 hour before partitioning between ethyl acetate (200ml) and saturated sodium hydrogencarbonate (200ml). The aqueous layer was extracted twice with ethyl acetate (100ml) and the combined organic layers were dried over magnesium sulfate and then concentrated *in vacuo* to yield 4-[[[2,4-dimethoxy-
 15 benzyl)-(morpholine-4-carbonyl)-amino]-methyl]-1-(tetrahydro-pyran-2-yl)-1H-pyrazole-3-carboxylic acid ethyl ester (1.66g) as a yellow oil. LC-MS (Method B): $R_T = 2.27$ minutes, 404.17 (M+H)⁺.

REFERENCE EXAMPLE 61

4-Amino-N-benzyl-3-nitro-benzenesulfonamide

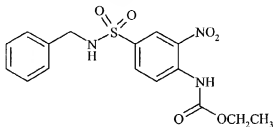


- 20 To a stirred suspension of (4-Benzylsulfamoyl-2-nitro-phenyl)-carbamic acid ethyl ester (1.50g, Reference Example 62) in ethanol (30ml) was added 2M sodium hydroxide solution (5.93ml) and the reaction heated at 75°C for 2 hours. The reaction mixture was cooled to ambient temperature, poured onto ice-water and acidified to pH3 with 2M hydrochloric acid (30ml). The resultant precipitate was

collected by filtration and dried *in vacuo* to give 4-amino-N-benzyl-3-nitro-benzenesulfonamide (1.01g) as a yellow solid. LC-MS (METHOD J): $R_T = 3.41$ minutes, 308.22 (M+H)⁺.

REFERENCE EXAMPLE 62

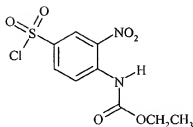
5 (4-Benzylsulfonyl-2-nitro-phenyl)-carbamic acid ethyl ester



- To a stirred solution of (4-chlorosulfonyl-2-nitro-phenyl)-carbamic acid ethyl ester (2g, Reference Example 63) in dichloromethane (50ml) at 0°C, under a nitrogen atmosphere, was added diisopropylethylamine (2.71ml) and benzylamine (0.850ml). The reaction was warmed to ambient temperature and stirred for 12 hours. The reaction mixture was then washed with water (2x20ml) and brine (2x20ml), dried over magnesium sulfate, filtered and the filtrate concentrated *in vacuo* to give the title compound (2.29g) as a brown solid. LC-MS (METHOD J): $R_T = 3.83$ minutes, 380.12 (M+H)⁺.
- 10

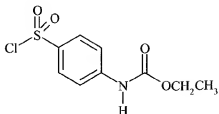
REFERENCE EXAMPLE 63

15 (4-Chlorosulfonyl-2-nitro-phenyl)-carbamic acid ethyl ester



- To a stirred suspension of (4-chlorosulfonyl-phenyl)-carbamic acid ethyl ester (5g, Reference Example 64) in concentrated sulfuric acid (25ml) at 0°C, was added dropwise a suspension of sodium nitrate (1.61g) in concentrated sulfuric acid and the reaction stirred for 3 hours. The reaction mixture was then poured onto ice, the resultant precipitate collected by filtration and dried *in vacuo* to give (4-chlorosulfonyl-2-nitro-phenyl)-carbamic acid ethyl ester (4.80g) as a yellow solid. LC-MS (METHOD B): $R_T = 3.32$ minutes, 307.08 (M-H)⁻.
- 25

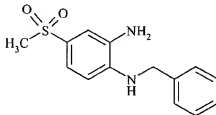
REFERENCE EXAMPLE 64

(4-Chlorosulfonyl-phenyl)-carbamic acid ethyl ester

- To a stirred solution of chlorosulfonic acid (20ml) at 0°C, was added *N*-phenylurethane (9.90g) at such a rate that the temperature did not exceed 20°C. The reaction was then heated at 60°C for 3 hours, cooled to ambient temperature and poured carefully onto ice. The resultant precipitate was collected by filtration and dried *in vacuo* to give (4-chlorosulfonyl-phenyl)-carbamic acid ethyl ester (14.50g) as an off-white solid. LC-MS (METHOD B): $R_T = 3.11$ minutes, 284.23 (M+H)⁺.

REFERENCE EXAMPLE 65

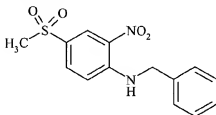
- 10 N*1*-Benzyl-4-methanesulfonyl-benzene-1,2-diamine



- A stirred solution of benzyl-(4-methanesulfonyl-2-nitro-phenyl)-amine (0.300g, Reference Example 66) and tin chloride (1.86g) in ethanol (5 ml) was heated in a Smith Creator microwave at 140°C for 10 minutes. The reaction mixture was basified using saturated sodium hydrogen carbonate solution to pH 8 and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give N*1*-benzyl-4-methanesulfonyl-benzene-1,2-diamine (0.255g) as a pale brown solid. LC-MS (METHOD B): $R_T = 2.74$ minutes, 275.20 (M-H)⁻.

REFERENCE EXAMPLE 66

- 20 Benzyl-(4-methanesulfonyl-2-nitro-phenyl)-amine

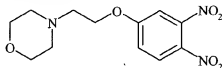


To a stirred suspension of (4-fluoro-2-nitrophenyl)methylsulfone (0.50g) and sodium hydrogen carbonate (0.575g) in ethanol and water (3:2) (30ml) was added benzylamine (0.374ml) and the

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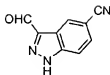
reaction stirred for 16 hours. The reaction mixture was then poured onto ice water, the resultant precipitate collected by filtration and dried *in vacuo* to give benzyl-(4-methanesulfonyl-2-nitro-phenyl)-amine (0.660g) as a yellow solid. LC-MS (METHOD B): $R_T = 2.97$ minutes, 307.04 (M+H)⁺.

5

REFERENCE EXAMPLE 674-[2-(3,4-Dinitro-phenoxy)-ethyl]-morpholine

- 10 A mixture of 3,4-dinitrophenol (250mg), 4-(2-chloroethyl)morpholine hydrochloride (252mg) and potassium carbonate (375mg) in dimethylformamide (3ml) was heated at 120°C for 20 minutes in a Personal Chemistry Smith Creator microwave. The reaction mixture was partitioned between ethyl acetate and water and the organic layer dried over magnesium sulfate, filtered and the filtrate concentrated *in vacuo* to give 4-[2-(3,4-dinitro-phenoxy)-ethyl]-morpholine (319mg) as a yellow oil. LC-MS (METHOD B): $R_T = 2.13$ minutes, 298 (M+H)⁺.

15

REFERENCE EXAMPLE 683-Formyl-1H-indazole-5-carbonitrile

- 20 To a suspension of 5-cyanoindole (3.93g) and sodium nitrite (19.07g) in water was added 6M hydrochloric acid slowly until the pH was less than 2. The suspension was then stirred for 3 hours at ambient temperature. The mixture was then extracted with ethyl acetate, dried over magnesium sulfate, filtered and the filtrate concentrated *in vacuo* to give 3-formyl-1H-indazole-5-carbonitrile (4.5g) as a pale brown solid. LC-MS (METHOD B): $R_T = 2.47$ minutes, 172.29 (M+H)⁺.

25

IN VITRO TEST PROCEDURESA. IN VITRO TEST PROCEDURES FOR SYK

30

1. Inhibitory effects of compounds on SYK kinase

Inhibitory effects of compounds on SYK kinase were determined using a time-resolved fluorescent assay.

- 5 The catalytic domain of SYK kinase (residues A340-N635) was expressed as a fusion protein in yeast cells and purified to homogeneity. Kinase activity was determined in 50mM Tris-HCl buffer pH 7.0 containing 50mM NaCl, 5mM MgCl₂, 5mM MnCl₂, 1μM adenosine triphosphate and 10μM synthetic peptide Biotin-(β-Alanine)₃-DEEDYEIPP-NH₂. Enzyme reactions were terminated by the addition of buffer containing 0.4M KF, 133mM EDTA, pH 7.0, containing a streptavidin-XL665 conjugate and a
- 10 monoclonal phosphospecific antibody conjugated to a europium cryptate (Eu-K). Features of the two fluorophores, XL-665 and Eu-K are given in G.Mathis et al., Anticancer Research, 1997, 17, pages 3011-3014. The specific long time signal of XL-665, produced only when the synthetic peptide is phosphorylated by SYK, was measured on a Packard Discovery Microplate analyzer or on an LJJL Biosystems Analyst AD microplate reader. Inhibition of SYK activity with compounds of the
- 15 invention was expressed as percentage inhibition of control activity exhibited in the absence of test compounds. Particular compounds of the invention inhibit SYK activity with IC₅₀s in the range 100 micromolar to 0.1 nanomolar. Preferred compounds of the invention inhibit SYK activity with IC₅₀s in the range 5000 nanomolar to 0.1 nanomolar. Particularly preferred compounds of the invention inhibit SYK activity with IC₅₀s in the range 1000 nanomolar to 0.1 nanomolar. Especially preferred
- 20 compounds of the invention inhibit SYK activity with IC₅₀s in the range 100 nanomolar to 0.1 nanomolar. More especially preferred compounds of the invention inhibit SYK activity with IC₅₀s in the range 10 nanomolar to 0.1 nanomolar.

- 25 2. Antigen-induced degranulation of Rat Bosophilic leukemia (RBL) cells as measured by [³H] 5-hydroxytryptamine (serotonin) release

2.1 Cell culture, labelling of RBL-2H3 cells and performance of assay.

- 30 Method A: For each 24-well culture plate to be set up, 6 x 10⁶ cells RBL-2H3 cells were washed and resuspended in 15 mL DMEM-10 containing 25μl of 1mCi/ mL [³H]-serotonin (0.5μCi/ mL final concentration) and 1μg/ mL (15mL) of anti-DNP IgE. 0.5 mL of cell suspension was added into each well of a 24-well plate. Cells were incubated for 2 days at 37°C, until they have reached confluence. The medium was gently aspirated from each well and the cells were then washed with assay buffer. A

final volume of 200mL of assay buffer (+ or - the test compounds at the appropriate concentrations) was then added to each of three replicate wells. 100ng/ mL of DNP (antigen) was then added to all wells (excluding negative control wells i.e. to measure spontaneous [³H]-serotonin release in the absence of receptor cross-linking). The cells were incubated for 30 minutes at 37°C and the reaction was stopped by transferring 100µl of the supernatant from each sample into a liquid scintillation microtitre plate kept on ice. 200µl of scintillant-40 was then added to each well of the microtitre plate and the plate was read on a Topcount Liquid Scintillation Counter.

Method B: RBL-2H3 cells are maintained in T75 flasks at 37°C and 5%CO₂, and passaged every 3-4 days. To harvest cells, 5 ml trypsin-EDTA is used to rinse the flask once, then 5 ml trypsin is added to each flask, and incubated at room temperature for 2 minutes. Cells are transferred to a tube with 14ml medium, spun down at 1100 rpm RT for 5 minutes and resuspended at 2x10⁵/ml. Cells are sensitized by adding 1µl of DNP-specific IgE (1 mg/ml stock solution) to every 10 ml of cells. 200µl of cells are added to each well of a flat-bottom 96 well plate (40,000 cells/well), and the plate incubated overnight at 37°C and 5%CO₂. The next day compounds are prepared in 100% DMSO at 10mM. Each compound is then diluted 1:100 in assay buffer and then diluted further in 1% DMSO-assay buffer to obtain final concentrations of 0.03-30µM. 80µl assay buffer (Hank's Balanced Salt Solution with Ca⁺⁺/Mg⁺⁺, 2 mg/ml glucose, 0.03% BSA) is added to each well, followed by 10µl of diluted compound. Incubation follows for 5 minutes. 10µl of DNP-HSA (100ng/ml) is added to each well and incubated at 37°C (no CO₂) for 30 minutes. As one control, 1% DMSO alone (no compound) is added to a set of wells to determine total release. As another control, buffer is added instead of DNP-HSA to another set of wells to determine the assay background. After 30 minutes incubation, the supernatants are transferred to a new 96-well plate. Add 50µl supernatant to each well of an assay plate. Add 100µl of substrate solution (5 mM PNAG in 0.4M citric acid, 0.2M Na₂HPO₄) to each well and incubate at 37°C for 90 minutes. Add 50µl of 0.4 M glycine solution to stop the reaction and the plate is read at 405 nm on a Molecular Devices SpectraMax 250 plate reader.

2.2 Calculation of results

30 Method A

- (i) The mean \pm s.e.m. of each set of triplicate wells was calculated.
- (ii) Maximum response was the positive control wells containing antigen (10ng/mL) but no compound.
- (iii) Minimum response was the control wells containing no antigen and no compound.
- (iv) Using these values as the maximum (100%) and minimum (0%) values respectively, the data was normalised to give a percentage of the maximum response.

(v) A dose response curve was plotted and the IC₅₀ of the compound was calculated.

Method B

(i) The mean \pm SD of each set of triplicate wells was calculated.

- 5 (ii) Maximum response was the positive control wells containing antigen (100ng/mL) but no compound.

(iii) Minimum response was the control wells containing buffer (no antigen) and no compound.

- (iv) Using these values as the maximum (100%) and minimum (0%) values respectively, the experimental data was calculated to yield a percentage of the maximum response (designated % control).
- 10

(v) A dose response curve was plotted and the IC₅₀ of the compound was calculated using Prism GraphPad software and nonlinear least squares regression analysis.

B. IN VITRO TEST PROCEDURES FOR KDR

15

1. Inhibitory effects of compounds on KDR

The inhibitory effect of the compounds is determined in a test of phosphorylation of a substrate by the enzyme KDR in vitro by the flasplate technique (96-well plate, NEN).

- 20 The cytoplasmic domain of human KDR enzyme is cloned in the form of a GST fusion into the baculovirus expression vector pFastBac. The protein is expressed in the SF21 cells and purified to about 60% homogeneity.

The kinase activity of KDR is measured in 20mM MOPS, 10mM MgCl₂, 10mM MnCl₂, 1mM DTT, 2.5mM EGTA, 10mM β -glycerophosphate, pH 7.2 in the presence of 10mM MgCl₂, 100 μ M Na₃VO₄,

- 25 1 mM NaF. 10 μ l of the compound are added to 70 μ l of kinase buffer containing 100ng of KDR enzyme at 4°C. The reaction is initiated by adding 20 μ l of solution containing 2 μ g of substrate (fragment SH2-SH3 of PLC γ expressed in the form of a GST fusion protein), 2 μ Ci γ 33P[ATP] and 2 μ M cold ATP. After incubating for 1 hour at 37°C, the reaction is quenched by adding 1 volume (100 μ l) of 200mM EDTA. The incubation buffer is removed and the wells are washed three times with
- 30 300 μ l of PBS. The radioactivity is measured in each well using a Top Count NXT instrument (Packard).

Background noise is determined by measuring the radioactivity in wells in quadruplet containing radioactive ATP and the substrate alone.

- An activity control is measured in wells in quadruplet containing all the reagents (γ 33P-[ATP], KDR and the substrate PLC γ) and in the absence of compound.
- 35

The inhibition of the KDR activity with the compound of the invention is expressed as a percentage of inhibition of the control activity determined in the absence of compound.

The compound SU5614 (Calbiochem) (1 μ M) is included in each plate as inhibition control.

The IC₅₀ values for the compounds are calculated by plotting the dose-response curves. The IC₅₀

- 5 corresponds to the concentration of compound that induces a 50% inhibition of the kinase activity. Particular compounds of the invention inhibit KDR activity with IC₅₀s in the range 100 micromolar to 10 nanomolar. Preferred compounds of the invention inhibit KDR activity with IC₅₀s in the range 3000 nanomolar to 10 nanomolar. Particular preferred compounds of the invention inhibit KDR activity with IC₅₀s in the range 300 nanomolar to 10 nanomolar.

10

II) Cellular activity on endothelial cells

1) Inhibition of the VEGF-dependent proliferation of HDMECs

- 15 The anti-KDR activity of the molecules is assessed by incorporating [14C]-thymidine into HDMECs (Human Dermal Microvascular Endothelial Cells) in response to VEGF. HDMECs (Promocell, passage 5 to 7) are inoculated in 100 μ l at 5000 cells per well in Cytostar (Amersham) 96-well plates precoated with attachment factor (AF, Cascad Biologics) at 37°C, 5% CO₂, on day 1. On day 2, the complete medium (basal medium supplemented with 5% FCS and a mixture of
- 20 growth factors) is replaced with minimum medium (basal medium supplemented with 5% FCS) and the cells are incubated for 24 hours. On day 3, the medium is replaced with 200 μ l of fresh medium that has or has not been supplemented with 100 ng/ml of VEGF (R&D System) and containing or not containing the compound of the invention and 0.1 μ Ci [14C]-thymidine. The cells are incubated at 37°C under 5% CO₂ for 4 days. The incorporation of [14C]-thymidine is then quantified by counting the radioactivity.
- 25 The tests are performed in 3 wells. The final concentration of DMSO in the test is 0.1%. The % of inhibition is calculated as follows:
$$\frac{[\text{cpm}(\text{+VEGF}) - \text{cpm}(\text{+VEGF} + \text{cpd})]}{[\text{cpm}(\text{+VEGF}) - \text{cpm}(\text{BM}5\%\text{FCS})]} \times 100.$$

2) Inhibition of the production of TF (Tissue factor) by endothelial cells in response to VEGF

30

The endothelial cells are inoculated at 20 000 cells per well in a 96-well plate precoated with attachment factor. After culturing for 8 hours, the medium is changed and the cells are preincubated with the compounds (0.1% DMSO final) in basal medium for 16 hours. The synthesis of the TF (tissue factor) is induced by adding VEGF (100 ng/ml final). After incubating for 6 hours, the cells are rinsed

35 and lysed. The tissue factor is then detected by means of the Imubind ELISA test.

3) Effect of the molecules on the VEGF-independent growth of HDMECs

The HDMECs (5000 cells per well) are inoculated in complete medium in Cytostar (Amersham) 96-well plates precoated with attachment factor (AF, Cascade Biologics) at 37°C, 5% CO₂, on day 1.

- 5 The whole medium is then removed and the cells are incubated in 200µl of complete medium containing the molecules of the invention and [¹⁴C]-thymidine (0.1µCi). The incorporation of the [¹⁴C]-thymidine is measured using a Wallac counter after incubating for 3 days. The % of inhibition is calculated as follows: $\frac{\text{cpm}(\text{CM}) - \text{cpm}(\text{CM} + \text{cpd})}{\text{cpm}(\text{CM})} \times 100$.
- 10 Table 5 below gives the results obtained in the above tests for the products indicated as examples in the present patent application.

TABLE 5

Example No.	IC ₅₀ (µM) on inhibition of the phosphorylation of PLCγ by KDR	% of inhibition of the phosphorylation of PLCγ by KDR (product tested at a concentration of 10µM)
14	1.2	
15	0.8	
16	2	
20	3.4	
21	-	35
1	0.47	
2	0.45	
3	-	91.8
4	0.45	
5	-	91.9
6	0.33	
7	0.72	
8	0.67	
9	0.35	

10	0.34	
11	0.26	
12	0.16	
13	0.61	
18	-	91.2
23	2	

The pharmacological results obtained in the above tests for products indicated in examples in the present application are given in the table 6 below, the degrees of activities of the products being indicated by + signs according to the ranges of activity indicated in the table, i.e.:

+ for an activity of greater than 3 micromolar

5 ++ for an activity of between 0.3 and 3 micromolar

+++ for an activity of less than 0.3 micromolar

TABLE 6

Example No.	Molecular formula	Molecular weight	Activity
			+ : $IC_{50} > 3 \mu M$
			++ : $0.3 \mu M < IC_{50} < 3 \mu M$
			+++ : $IC_{50} < 0.3 \mu M$
28	C22H18N6O3S	446.49	+++
29	C20H21N5O2	363.42	++
30	C22H16BrN5O	446.31	+++
31	C23H19N5O3S	445.50	+++
32	C26H19N5O	417.47	++
33	C23H16F3N5O	435.41	++
34	C20H15N5OS	373.44	++
35	C24H22N6O	410.48	++
36	C26H30N6O3	474.56	++
37	C22H16N6O3	412.41	+++
38	C21H16N6O	368.40	++
39	C22H16BrN5O	446.31	++
40	C23H19N5O2	397.44	++
41	C23H17N5O3	411.42	++
42	C24H17N5OS	423.50	++
43	C21H19N7O	385.43	++
44	C23H16F3N5O2	451.41	++

45	C23H19N5O	381.44	+++
46	C21H17N5OS	387.46	++
47	C23H16F3N5O	435.41	++
48	C28H21N5O2	459.51	++
49	C23H16F3N5O2	451.41	++
50	C21H23N5O2	377.45	++
51	C20H17N7O	371.40	++
52	C25H23N5O	409.49	++
53	C22H19N5O2	385.43	++
54	C24H17N5OS	423.50	++
55	C26H24N6O3	468.52	++
56	C21H15C1N6O	402.84	+++
57	C24H17N5OS2	455.56	++
58	C24H19N5O2	409.45	+++
59	C23H16N6O	392.42	++
60	C24H16C1N5OS	457.94	+
61	C23H16F3N5O	435.41	+
62	C23H19N5OS	413.50	+++
63	C24H17N5OS	423.50	+++
64	C21H21N5O2	375.43	++
65	C24H19N5O3	425.45	++
66	C20H15N5O2	357.37	++
67	C22H16N6O3	412.41	++
68	C20H15N5OS	373.44	++
69	C24H21N5O	395.47	++
70	C24H19N7O	421.46	++
71	C23H19N5O	381.44	+++
72	C22H16C1N5O	401.86	+++

73	C22H18N6O3S	446.49	++
74	C20H21N5O2	363.42	+
75	C22H16BrN5O	446.31	+
76	C26H19N5O	417.47	+
77	C20H15N5OS	373.44	+
78	C24H22N6O	410.48	+
79	C22H16N6O3	412.41	+
80	C21H16N6O	368.40	++
81	C22H16BrN5O	446.31	+
82	C23H19N5O2	397.44	++
83	C24H17N5OS	423.50	+
84	C28H21N5O2	459.51	+
85	C23H16F3N5O2	451.41	+
86	C21H15ClN6O	402.84	+
87	C24H19N5O2	409.45	+
88	C23H16F3N5O	435.41	+
89	C23H19N5OS	413.50	+++
90	C20H15N5O2	357.37	++
91	C22H16N6O3	412.41	++
92	C24H21N5O	395.47	++
93	C22H16ClN5O	401.86	+
94	C21H15N5O	353.38	++
95	C22H17N5O	367.41	+
96	C23H19N5O	381.44	+
97	C20H14N4	310.36	+
98	C20H12Cl2N4	379.25	+
99	C24H16N4	360.42	+
100	C20H13FN4	328.35	++
101	C20H13ClN4	344.80	+
102	C21H16N4O	340.39	++
103	C20H12ClFN4	362.79	++
104	C20H12Cl2N4	379.25	+
105	C26H16N4S2	448.57	+

106	C26H18N4	386.46	+
107	C21H16N4	324.39	+
108	C21H16N4	324.39	++
109	C21H16N4	324.39	++
110	C18H12N4S	316.39	++
111	C21H13F3N4	378.36	+
112	C21H13F3N4	378.36	+
113	C20H13ClN4	344.80	++
114	C21H16N4O	340.39	++
115	C22H18N4	338.41	++
116	C22H18N4	338.41	+
117	C21H14N4O2	354.37	++
118	C24H22N4	366.47	+
119	C20H20N4	316.41	++
120	C22H18N4O2	370.41	++
121	C20H14N4O	326.36	++
122	C20H14N4O	326.36	++
123	C20H12Cl2N4	379.25	+
124	C21H13F3N4O	394.36	+
125	C22H16N4O	352.40	+
126	C22H14N4S	366.45	+
127	C23H20N4O3	400.44	++
128	C20H14N4OS	358.42	++
129	C22H16N4O	352.40	+
130	C27H20N4O	416.48	+
131	C26H17FN4	404.45	+
132	C22H14N4S	366.45	+
133	C21H16N4O	340.39	++

134	C22H18N4S	370.48	+
135	C20H12F2N4	346.34	++
136	C21H13F3N4O	394.36	+
137	C21H15FN4	342.38	++
138	C22H15FN4	354.39	+
139	C22H15ClN4	370.84	+
140	C23H18N4O2	382.42	+
141	C21H16N4O	340.39	++
142	C18H12N4O	300.32	++
143	C27H20N4O	416.48	+
144	C23H20N4	352.44	++
145	C21H16N4O2S	388.45	+
146			++
147			++
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226			+
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228			+

C. IN VITRO TEST PROCEDURES FOR ITK

5 1. Inhibitory effects of compounds on ITK kinase

Inhibitory effects of compounds on ITK kinase were determined using a Fluorescence Polarization assay.

ITK kinase was produced with Baculovirus expression system.

10 1.1 Assay Technology

The assay measures the autophosphorylation of the ITK kinase. The assay is configured based on Fluorescence Polarization method. The enzyme is incubated with ATP and compound. After incubation, a mixture containing fluorescence labeled phospho-peptide tracer and anti-phospho-tyrosine antibody (CoreHTS tyrosine kinase assay kit, P2837, Panvera) is added in order to generate

- 15 the specific signal that is reversely proportional to the phosphorylation of the enzyme. The phosphorylated ITK generated from the kinase reaction will compete specifically for the antibody and release the fluorescence labeled tracer. Inhibition of ITK kinase activity will result in increased FP value.

20 1.2 Assay Conditions

The assay is run in BD black 384-shallow well plate. For enzyme reaction, the final reagent concentration/well: 16.5nM ITK enzyme, 50μM ATP, 20 mM Hepes (pH 7.5), 0.15M NaCl, 3mM

MgCl₂, 1mM MnCl₂, 0.01% Triton X-100, 1mM DTT, 5% glycerol and 0.1% γ-globulin. Incubation time: 45 minutes. Temperature: 25°C. Reaction volume: 10μL. For immuno-reaction, add 10μL of Stop-Detection mixture containing 10mM EDTA, 1:2 dilution of antibody and 1:4 dilution of tracer in 1x dilution buffer (Panvera). Incubation time: 90 minutes at 37°C followed by room temperature 60 minutes.

1.3 Assay Procedure:

1. Add 5.0μL ATP solution to each well of the black 384-shallow well plate.
2. Add 1.0μL compounds or 1% DMSO in TBS buffer.
3. Start Reaction by adding 5.0μL enzyme solution.
4. Incubate at 25°C for 45 minutes.
5. Add 10μL of stop-detection solution.
6. Incubate for 90 minutes at 37°C followed by incubation at room temperature for 60 minutes.
7. Read by LJI Acquest at FP mode using a fluorescence filter set ($E_x = 485 \text{ nm}$, $E_m = 535 \text{ nm}$) with FL dichroic mirror. Integration Time: 200,000 μs. G factor instrument

$$\text{dependent [G factor} = \frac{(S_{\text{TracerOnly}} - S_{\text{Buffer}})}{(S_{\text{TracerOnly}} + S_{\text{Buffer}})}$$

Inhibition of ITK activity with compounds of the invention was expressed as percentage inhibition of control activity determined in the absence of test compounds.

The IC₅₀ values for the compounds are calculated by plotting the dose-response curves. The IC₅₀ corresponds to the concentration of compound that induces a 50% inhibition of the kinase activity. Particular compounds of the invention inhibit ITK activity with IC₅₀s in the range 100 micromolar to 1 micromolar.

IN VIVO TEST PROCEDURES

A. *IN VIVO* TEST PROCEDURES FOR SYK

1. Inhibition of antigen-dependent passive cutaneous anaphylaxis.

Compounds of the invention were assessed in the Balb/c mouse passive cutaneous anaphylaxis (PCA) model. The model used in these *in vivo* studies mimics relevant features of mast cell-driven antigen-dependent activation and functional responses. These studies demonstrated that compounds of the invention inhibit the increase in edema observed in the sensitized mouse ear following antigen exposure.

Protocol for sensitization and challenge.

Balb/c mice were sensitized in the right ear on day 0 with monoclonal anti-DNP IgE (25µg) administered intradermally in the ear pinnae. The left ear was injected with PBS to serve as a control.

- 5 Sixteen to twenty hours after sensitization, mice were antigen challenged with 150 µg DNP-albumin administered i.v.

Protocol for dosing and calculation of results

- Test drug was administered orally 15-60 minutes before DNP-albumin antigen challenge. Doses of compound were administered at half log divisions between 3 and 100 mg/kg. A control set of mice was administered vehicle alone, and thereafter treated identically. Ear thickness was measured at t= 0, 15, 30 or 60 minutes after DNP-albumin antigen challenge, in both ears, by digital calipers and expressed in units of mm x 0.01. Ear thickness at t=0 was recorded to serve as a baseline. The net increase in both the right and left ear was calculated by subtracting the values at t=0 from those at t=15, 30 or 60 minutes. Percent inhibition of ear edema was then calculated as [ear thickness of control-(ear thickness of right ear-ear thickness of left ear)]/ear thickness of control x 100 for each time point measured.
- 10
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Results

- 20 (i) The compound demonstrated dose-dependent inhibition of ear edema following oral administration of 3-100 mg/kg. Inhibition of ear edema was observed at t= 15, 30 and 60 minutes after antigen challenge.

These results indicate that compounds of the invention inhibit mast cell activation and functional responses when given orally in a mouse model of passive cutaneous anaphylaxis.

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2. Antigen-induced degranulation of Rat Basophilic Leukemia (RBL) cells as measured by [³H] 5-hydroxytryptamine (serotonin) release

- 30 2.1 Cell culture, labelling of RBL-2H3 cells and performance of assay.

Method A: For each 24-well culture plate to be set up, 6×10^6 cells RBL-2H3 cells were washed and resuspended in 15 mL DMEM-10 containing 25µl of 1mCi/ mL [³H]-serotonin (0.5µCi/ mL final concentration) and 1µg/ mL (15mL) of anti-DNP IgE. 0.5 mL of cell suspension was added into each well of a 24-well plate. Cells were incubated for 2 days at 37°C, until they have reached confluence. The medium was gently aspirated from each well and the cells were then washed with assay buffer. A

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final volume of 200mL of assay buffer (+ or - the test compounds at the appropriate concentrations) was then added to each of three replicate wells. 100ng/ mL of DNP (antigen) was then added to all wells (excluding negative control wells i.e. to measure spontaneous [³H]-serotonin release in the absence of receptor cross-linking). The cells were incubated for 30 minutes at 37°C and the reaction was stopped by transferring 100µl of the supernatant from each sample into a liquid scintillation microtitre plate kept on ice. 200µl of scintillant-40 was then added to each well of the microtitre plate and the plate was read on a Topcount Liquid Scintillation Counter.

Method B: RBL-2H3 cells are maintained in T75 flasks at 37°C and 5%CO₂, and passaged every 3-4 days. To harvest cells, 5 ml trypsin-EDTA is used to rinse the flask once, then 5 ml trypsin is added to each flask, and incubated at room temperature for 2 minutes. Cells are transferred to a tube with 14ml medium, spun down at 1100 rpm RT for 5 minutes and resuspended at 2x10⁵/ml. Cells are sensitized by adding 1µl of DNP-specific IgE (1 mg/ml stock solution) to every 10 ml of cells. 200µl of cells are added to each well of a flat-bottom 96 well plate (40,000 cells/well), and the plate incubated overnight at 37°C and 5%CO₂. The next day compounds are prepared in 100% DMSO at 10mM. Each compound is then diluted 1:100 in assay buffer and then diluted further in 1% DMSO-assay buffer to obtain final concentrations of 0.03-30µM. 80µl assay buffer (Hank's Balanced Salt Solution with Ca⁺⁺/Mg⁺⁺, 2 mg/ml glucose, 0.03% BSA) is added to each well, followed by 10µl of diluted compound. Incubation follows for 5 minutes. 10µl of DNP-HSA (100ng/ml) is added to each well and incubated at 37°C (no CO₂) for 30 minutes. As one control, 1% DMSO alone (no compound) is added to a set of wells to determine total release. As another control, buffer is added instead of DNP-HSA to another set of wells to determine the assay background. After 30 minutes incubation, the supernatants are transferred to a new 96-well plate. Add 50µl supernatant to each well of an assay plate. Add 100µl of substrate solution (5 mM PNAG in 0.4M citric acid, 0.2M Na₂HPO₄) to each well and incubate at 37°C for 90 minutes. Add 50µl of 0.4 M glycine solution to stop the reaction and the plate is read at 405 nm on a Molecular Devices SpectraMax 250 plate reader.

2.2 Calculation of results

30 Method A

- (i) The mean ± s.e.m. of each set of triplicate wells was calculated.
- (ii) Maximum response was the positive control wells containing antigen (10ng/mL) but no compound.
- (iii) Minimum response was the control wells containing no antigen and no compound.
- (iv) Using these values as the maximum (100%) and minimum (0%) values respectively, the data was normalised to give a percentage of the maximum response.

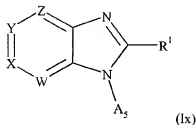
(v) A dose response curve was plotted and the IC₅₀ of the compound was calculated.

Method B

- (i) The mean \pm SD of each set of triplicate wells was calculated.
- 5 (ii) Maximum response was the positive control wells containing antigen (100ng/mL) but no compound.
- (iii) Minimum response was the control wells containing buffer (no antigen) and no compound.
- (iv) Using these values as the maximum (100%) and minimum (0%) values respectively, the experimental data was calculated to yield a percentage of the maximum response (designated %
- 10 control).
- (v) A dose response curve was plotted and the IC₅₀ of the compound was calculated using Prism GraphPad software and nonlinear least squares regression analysis.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a compound of general formula (Ix)



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wherein

X represents C-R² and W, Y and Z, which may be identical or different, represent CH or CR³; or

W represents CH, X represents N, Y represents CH or CR³, and Z represents CH or CR³; or

W represents N, X represents CH or CR², Y represents CH and CR³, and Z represents CH or CR³; or

- 10 W represents N, X represents CH or CR², Y represents N, and Z is CH or CR³; or

W represents N, X represents CH or CR², Y represents CH or CR³, and Z represents N; or

W represents N, X represents N, Y represents CH or CR³, and Z represents CH or CR³;

A₅ represents H or alkyl;

R¹ represents aryl or heteroaryl, each optionally substituted by one or more groups selected from

- 15 carboxy, cyano, halo, haloalkyl, hydroxy, nitro, R⁴, -C(=O)R⁴, -C(=O)NY¹Y², -C(=O)OR⁴,
-N(R⁶)C(=O)R⁴, -N(R⁶)C(=O)NY¹Y², -N(R⁶)C(=O)OR⁴, -N(R⁶)SO₂R⁴, -N(R⁶)SO₂NY¹Y²,
-NY¹Y², -OR⁴, -OCF₂H, -OCF₃, -OC(=O)R⁴, -OC(=O)NY¹Y², -OS(O)_nR⁴, -S(O)_nR⁴,
-S(O)_nNY¹Y² and -S(O)_nOR⁴;

R² and R³ are such that:

- 20 R² and R³, which may be identical or different, represent H, carboxy, cyano, halo, haloalkyl, hydroxy,
nitro, R⁴, -C(=O)R⁴, -C(=O)NY¹Y², -C(=O)OR⁴, -NY¹Y², -N(R⁶)C(=O)R⁴, -N(R⁶)C(=O)NY¹Y²,
-N(R⁶)C(=O)OR⁴, -N(R⁶)SO₂R⁴, -N(R⁶)SO₂NY¹Y², -OR⁴, -OCF₂H, -OCF₃, -OC(=O)R⁴,
-OC(=O)NY¹Y², -S(O)_nR⁴, -S(O)_nNY¹Y² or -S(O)_nOR⁴; or

R² represents H, carboxy, cyano, halo, haloalkyl, hydroxy, nitro, R⁴, -C(=O)R⁴, -C(=O)NY¹Y²,

- 25 -C(=O)OR⁴, -NY¹Y², -N(R⁶)C(=O)R⁴, -N(R⁶)C(=O)NY¹Y², -N(R⁶)C(=O)OR⁴, -N(R⁶)SO₂R⁴,
-N(R⁶)SO₂NY¹Y², -OR⁴, -OCF₂H, -OCF₃, -OC(=O)R⁴, -OC(=O)NY¹Y², -S(O)_nR⁴, -S(O)_nNY¹Y²
or -S(O)_nOR⁴ and R³ represents alkyl, haloalkyl, halogen and OR⁶; or

R² and R³ groups on adjacent carbon atoms may form a 5- to 6-membered carbon-based ring containing one or more heteroatoms, which may be identical or different, chosen from O, N and S, and which may be optionally substituted by alkyl;

R⁴ is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, each optionally

- 5 substituted with one or more substituents selected from alkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, halo, hydroxy, hydroxyalkyl, -C(=O)NY³Y⁴, -C(=O)OR⁶, -N(R⁶)C(=O)NY¹Y², -NY¹Y², -OR⁵ or alkyl substituted by -NY³Y⁴;

R⁵ is alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

- 10 R⁶ is alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

n is zero or an integer 1 or 2;

Y¹ and Y² are independently hydrogen, alkenyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl or alkyl optionally substituted by one or more groups selected from cyano, aryl,

- 15 heteroaryl, hydroxy, -C(=O)OR⁶, -C(=O)NY³Y⁴, -NY³Y⁴ and -OR⁵, or the group -NY¹Y² may form a cyclic amine;

Y³ and Y⁴ are independently hydrogen, alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl; or the group -NY³Y⁴ may form a cyclic amine; where

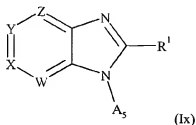
- 20 all the alkyl, alk, alkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl radicals present in the above radicals are optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, cyano, alkyl, alkoxy, acylamino (NH-COalk), -C(=O)OR⁶, -C(=O)R⁶, hydroxyalkyl, carboxyalkyl, S(O)_n-alk, S(O)_n-NH₂, S(O)_n-NH(alk), S(O)_n-N(alk)₂, CF₃, OCF₃, NO₂, arylalkoxy, aryl, heteroaryl, aryloxy, aryloxyalkyl, -C(=O)-NY³Y⁴ and NY³Y⁴ radicals, the latter
- 25 radicals containing alkyl, aryl and heteroaryl being themselves optionally substituted with one or more radicals chosen from halogen atoms and alkyl radicals, free, salified or esterified carboxyl radicals and acylamino radicals NH-C(O)R⁵,
- or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate; together with one or
- 30 more pharmaceutically acceptable carriers or excipients.

2. A pharmaceutical composition according to claim 1 wherein

R² and R³ form a group selected from -O-CH₂-O-, -O-CH₂-CH₂-O-, -CH₂-O-CH₂-,

-CH₂-N(R¹⁴)-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-C(CH₃)₂-CH₂-, -CH₂-O-CH₂-CH₂-,
 -CH₂-N(R¹⁴)-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-C(CH₃)₂-CH₂-CH₂-, -CH=CH-CH=CH-,
 -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH- and -CH=CH-CH=N, where R¹⁴ is H or alkyl.

- 5 3. A compound of general formula (Ix)



wherein

- X represents C-R² and W, Y and Z, which may be identical or different, represent CH or CR³; or
 10 W represents CH, X represents N, Y represents CH or CR³, and Z represents CH or CR³; or
 W represents N, X represents CH or CR², Y represents CH and CR³, and Z represents CH or CR³; or
 W represents N, X represents CH or CR², Y represents N, and Z is CH or CR³; or
 W represents N, X represents CH or CR², Y represents CH or CR³, and Z represents N; or
 W represents N, X represents N, Y represents CH or CR³, and Z represents CH or CR³;
 15 A₅ represents H or alkyl;

R¹ represents aryl or heteroaryl, each optionally substituted by one or more groups selected from
 carboxy, cyano, halo, haloalkyl, hydroxy, nitro, R⁴, -C(=O)R⁴, -C(=O)NY¹Y², -C(=O)OR⁴,
 -N(R⁶)C(=O)R⁴, -N(R⁶)C(=O)NY¹Y², -N(R⁶)C(=O)OR⁴, -N(R⁶)SO₂R⁴, -N(R⁶)SO₂NY¹Y²,
 -NY¹Y², -OR⁴, -OCF₂H, -OCF₃, -OC(=O)R⁴, -OC(=O)NY¹Y², -OS(O)_nR⁴, -S(O)_nR⁴,

- 20 -S(O)_nNY¹Y² and -S(O)_nOR⁴;

R² and R³ are such that:

R² and R³, which may be identical or different, represent H, carboxy, cyano, halo, haloalkyl, hydroxy,
 nitro, R⁴, -C(=O)R⁴, -C(=O)NY¹Y², -C(=O)OR⁴, -NY¹Y², -N(R⁶)C(=O)R⁴, -N(R⁶)C(=O)NY¹Y²,
 -N(R⁶)C(=O)OR⁴, -N(R⁶)SO₂R⁴, -N(R⁶)SO₂NY¹Y², -OR⁴, -OCF₂H, -OCF₃, -OC(=O)R⁴,

- 25 -OC(=O)NY¹Y², -S(O)_nR⁴, -S(O)_nNY¹Y² or -S(O)_nOR⁴; or

R² represents H, carboxy, cyano, halo, haloalkyl, hydroxy, nitro, R⁴, -C(=O)R⁴, -C(=O)NY¹Y²,
 -C(=O)OR⁴, -NY¹Y², -N(R⁶)C(=O)R⁴, -N(R⁶)C(=O)NY¹Y², -N(R⁶)C(=O)OR⁴, -N(R⁶)SO₂R⁴,

$-\text{N}(\text{R}^6)\text{SO}_2\text{NY}^1\text{Y}^2$, $-\text{OR}^4$, $-\text{OCF}_2\text{H}$, $-\text{OCF}_3$, $-\text{OC}(=\text{O})\text{R}^4$, $-\text{OC}(=\text{O})\text{NY}^1\text{Y}^2$, $-\text{S}(\text{O})_n\text{R}^4$, $-\text{S}(\text{O})_n\text{NY}^1\text{Y}^2$ or $-\text{S}(\text{O})_n\text{OR}^4$ and R^3 represents alkyl, haloalkyl, halogen and OR^6 ; or

R^2 and R^3 groups on adjacent carbon atoms may form a 5- to 6-membered carbon-based ring containing one or more heteroatoms, which may be identical or different, chosen from O, N and S, and which may be optionally substituted by alkyl;

R^4 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, each optionally substituted with one or more substituents selected from alkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, halo, hydroxy, hydroxyalkyl, $-\text{C}(=\text{O})\text{NY}^3\text{Y}^4$, $-\text{C}(=\text{O})\text{OR}^6$, $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{NY}^1\text{Y}^2$, $-\text{NY}^1\text{Y}^2$, $-\text{OR}^5$ or alkyl substituted by $-\text{NY}^3\text{Y}^4$;

- 10 R^5 is alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R^6 is alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

n is zero or an integer 1 or 2;

- 15 Y^1 and Y^2 are independently hydrogen, alkenyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl or alkyl optionally substituted by one or more groups selected from cyano, aryl, heteroaryl, hydroxy, $-\text{C}(=\text{O})\text{OR}^6$, $-\text{C}(=\text{O})\text{NY}^3\text{Y}^4$, $-\text{NY}^3\text{Y}^4$ and $-\text{OR}^5$, or the group $-\text{NY}^1\text{Y}^2$ may form a cyclic amine;

Y^3 and Y^4 are independently hydrogen, alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or

- 20 heteroarylalkyl; or the group $-\text{NY}^3\text{Y}^4$ may form a cyclic amine;

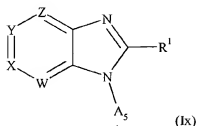
where

all the alkyl, alk, alkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl radicals present in the above radicals are optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, cyano, alkyl, alkoxy, acylamino ($\text{NH}-\text{COalk}$), $-\text{C}(=\text{O})\text{OR}^6$, $-\text{C}(=\text{O})\text{R}^6$,

- 25 hydroxyalkyl, carboxyalkyl, $\text{S}(\text{O})_n\text{-alk}$, $\text{S}(\text{O})_n\text{-NH}_2$, $\text{S}(\text{O})_n\text{-NH(alk)}$, $\text{S}(\text{O})_n\text{-N(alk)}_2$, CF_3 , OCF_3 , NO_2 , arylalkoxy, aryl, heteroaryl, aryloxy, aryloxyalkyl, $-\text{C}(=\text{O})\text{-NY}^3\text{Y}^4$ and NY^3Y^4 radicals, the latter radicals containing alkyl, aryl and heteroaryl being themselves optionally substituted with one or more radicals chosen from halogen atoms and alkyl radicals, free, salified or esterified carboxyl radicals and acylamino radicals $\text{NH}-\text{C}(\text{O})\text{R}^5$;

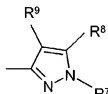
- 30 or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.

4. A compound of formula (Ix)



wherein

- 5 X represents $C-R^2$ and W, Y and Z, which may be identical or different, represent CH or CR^3 ; or W represents CH, X represents N, Y represents CH or CR^3 , and Z represents CH or CR^3 ; or W represents N, X represents CH or CR^2 , Y represents CH or CR^3 , and Z represents CH or CR^3 ; or W represents N, X represents CH or CR^2 , Y represents N, and Z is CH or CR^3 ; or W represents N, X represents CH or CR^2 , Y represents CH or CR^3 , and Z represents N; or
- 10 W represents N, X represents N, Y represents CH or CR^3 , and Z represents CH or CR^3 ;
 A_5 represents H or alkyl;



- R^1 is a pyrazolyl moiety in which R^7 is hydrogen or alkyl, and R^8 and R^9 are independently selected from hydrogen, carboxy, cyano, halo, haloalkyl, hydroxy, nitro, R^4 , $-C(=O)R^4$, $-C(=O)NY^1Y^2$, $-C(=O)OR^4$, $-N(R^6)C(=O)R^4$, $-N(R^6)C(=O)NY^1Y^2$, $-N(R^6)C(=O)OR^4$,
- 15 $-N(R^6)SO_2R^4$, $-N(R^6)SO_2NY^1Y^2$, $-NY^1Y^2$, $-OR^4$, $-OC(=O)R^4$, $-OC(=O)NY^1Y^2$, $-S(O)_nR^4$ and $-S(O)_2NY^1Y^2$; or R^8 and R^9 together with the carbon atoms to which they are attached form (i) a 5 to 8 membered carbocyclic ring optionally substituted by one or more carbocyclic ring substituents; (ii) a phenyl ring optionally substituted by one or more aryl group substituents; (iii) a 5 or 6 membered heteroaromatic ring in which one or more of the ring members is/are nitrogen, oxygen or sulfur and
- 20 which is optionally substituted by one or more groups selected from haloalkyl, hydroxy, halo, cyano, nitro, R^4 , $-C(=O)NY^1Y^2$, $-N(R^6)C(=O)R^4$, $-N(R^6)C(=O)NY^1Y^2$, $-N(R^6)SO_2R^4$, $-NY^1Y^2$ and $-OR^5$; or (iv) a 5 or 6 membered heterocyclic ring optionally substituted by alkyl or oxo, and containing a heteroatom-containing group selected from O, S, SO_2 , and NY^5 , where Y^5 is hydrogen, R^4 , $-C(=O)R^4$, $-C(=O)NY^1Y^2$, $-C(=O)OR^4$ or $-SO_2R^4$;

R^2 and R^3 are such that:

R^2 and R^3 , which may be identical or different, represent H, carboxy, cyano, halo, haloalkyl, hydroxy, nitro, R^4 , $-C(=O)R^4$, $-C(=O)NY^1Y^2$, $-C(=O)OR^4$, $-NY^1Y^2$, $-N(R^6)C(=O)R^4$, $-N(R^6)C(=O)NY^1Y^2$, $-N(R^6)C(=O)OR^4$, $-N(R^6)SO_2R^4$, $-N(R^6)SO_2NY^1Y^2$, $-OR^4$, $-OCF_2H$, $-OCF_3$, $-OC(=O)R^4$,

- 5 $-OC(=O)NY^1Y^2$, $-S(O)_nR^4$, $-S(O)_nNY^1Y^2$ or $-S(O)_nOR^4$; or

R^2 represents H, carboxy, cyano, halo, haloalkyl, hydroxy, nitro, R^4 , $-C(=O)R^4$, $-C(=O)NY^1Y^2$, $-C(=O)OR^4$, $-NY^1Y^2$, $-N(R^6)C(=O)R^4$, $-N(R^6)C(=O)NY^1Y^2$, $-N(R^6)C(=O)OR^4$, $-N(R^6)SO_2R^4$, $-N(R^6)SO_2NY^1Y^2$, $-OR^4$, $-OCF_2H$, $-OCF_3$, $-OC(=O)R^4$, $-OC(=O)NY^1Y^2$, $-S(O)_nR^4$, $-S(O)_nNY^1Y^2$ or $-S(O)_nOR^4$ and R^3 represents alkyl, haloalkyl, halogen and OR^6 ; or

- 10 R^2 and R^3 groups on adjacent carbon atoms may form a 5- to 6-membered carbon-based ring containing one or more heteroatoms, which may be identical or different, chosen from O, N and S, and which may be optionally substituted by alkyl;

R^4 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, each optionally substituted with one or more substituents selected from alkyl, aryl, cycloalkyl, heteroaryl,

- 15 heterocycloalkyl, halo, hydroxy, hydroxyalkyl, $-C(=O)NY^3Y^4$, $-C(=O)OR^6$, $-N(R^6)C(=O)NY^1Y^2$, $-NY^1Y^2$, $-OR^5$ or alkyl substituted by $-NY^3Y^4$;

R^5 is alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R^6 is alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl,

- 20 heterocycloalkyl or heterocycloalkylalkyl;

n is zero or an integer 1 or 2;

Y^1 and Y^2 are independently hydrogen, alkenyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, heterocycloalkylalkyl or alkyl optionally substituted by one or more groups selected from cyano, aryl, heteroaryl, hydroxy, $-C(=O)OR^6$, $-C(=O)NY^3Y^4$, $-NY^3Y^4$ and $-OR^5$, or the group $-NY^1Y^2$ may form

- 25 a cyclic amine;

Y^3 and Y^4 are independently hydrogen, alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl; or the group $-NY^3Y^4$ may form a cyclic amine;

where

all the alkyl, alk, alkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl

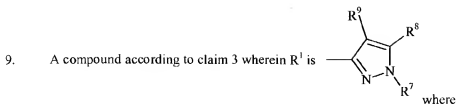
- 30 radicals present in the above radicals are optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, cyano, alkyl, alkoxy, acylamino ($NH-COalk$), $-C(=O)OR^6$, $-C(=O)R^6$, hydroxyalkyl, carboxyalkyl, $S(O)_n-alk$, $S(O)_n-NH_2$, $S(O)_n-NH(alk)$, $S(O)_n-N(alk)_2$, CF_3 , OCF_3 , NO_2 ,

arylalkoxy, aryl, heteroaryl, aryloxy, aryloxyalkyl, $-C(=O)-NY^3Y^4$ and NY^3Y^4 radicals, the latter radicals containing alkyl, aryl and heteroaryl being themselves optionally substituted with one or more radicals chosen from halogen atoms and alkyl radicals, free, salified or esterified carboxyl radicals and acylamino radicals $NH-C(O)R^5$;

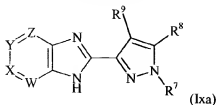
- 5 or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate; provided that the compound is other than 2-(2H-pyrazol-3-yl)-1H-benzimidazole; 2-(5-methyl-2H-pyrazol-3-yl)-1H-benzimidazole; 5-methyl-6-[2-(2H-pyrazol-3-yl)-3H-benzimidazol-5-yl]-4,5-dihydro-2H-pyridazin-3-one; 5-methyl-6-[2-(2H-pyrazol-3-yl)-1H-benzimidazol-4-yl]-4,5-dihydro-
- 10 2H-pyridazin-3-one; 3,5-bis(benzimidazol-2-yl)-1H-pyrazole; 5,6-dimethyl-2-(5-methyl-1H-pyrazol-3-yl)-1H-benzimidazole; 6-methyl-2-(5-methyl-1H-pyrazol-3-yl)-1H-benzimidazole; 5,6-dichloro-2-(5-methyl-1H-pyrazole-3-yl)-1H-benzimidazole; 5-nitro-2-(5-methyl-1H-pyrazole-3-yl)-1H-benzimidazole; 2-(5-methyl-1H-pyrazole-3-yl)-1H-benzimidazole-5-carboxylic acid; 2-(5-phenyl-1H-pyrazole-3-yl)-1H-benzimidazole; 5,6-dimethyl-2-(5-phenyl-1H-pyrazole-3-yl)-1H-
- 15 benzimidazole; 5-methyl-2-(5-phenyl-1H-pyrazole-3-yl)-1H-benzimidazole; 6-chloro-2-(5-methyl-1H-pyrazole-3-yl)-1H-benzimidazole; 5-chloro-2-(5-phenyl-1H-pyrazole-3-yl)-1H-benzimidazole; 5,6-dichloro-2-(5-phenyl-1H-pyrazole-3-yl)-1H-benzimidazole; N-[2-(5-isoquinolin-4-yl-1H-indazol-3-yl)-3H-benzimidazol-5-yl]-methanesulfonamide; 3-(1H-benzimidazol-2-yl)-5-(1H-indazol-4-yl)-1H-indazole, 3-[3-(1H-benzimidazol-2-yl)-1H-indazol-5-yl]-2-methoxyphenol; 4-[3-(1H-
- 20 benzimidazol-2-yl)-1H-indazol-5-yl]isoquinoline; 4-[3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-indazol-5-yl]-isoquinoline; 4-[3-(4-chloro-1H-benzimidazol-2-yl)-1H-indazol-5-yl]-isoquinoline; 4-[2-(1H-indazol-3-yl)-1H-benzimidazol-5-yl]-phenol; 3-[5-(4-methoxy-phenyl)-1H-benzimidazol-2-yl]-1H-indazole; 3-[5-(4-methoxy-phenyl)-1H-benzimidazol-2-yl]-1H-indazole; 3-[5-(3-methoxy-phenyl)-1H-benzimidazol-2-yl]-1H-indazole; 3-(1H-benzimidazol-2-yl)-5-
- 25 phenyl-1H-indazole; 2-(4-bromo-1-methyl-1H-pyrazol-3-yl)-1H-benzimidazole; 2-(5-*tert*-butyl-1H-pyrazol-3-yl)-1H-benzimidazole; 3-(1H-benzimidazol-2-yl)-6-(3-methoxy-phenyl)-1H-indazole; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid; 5-[[3-(1H-benzimidazol-2-yl)-1H-indazole-6-carbonyl]-amino]-2-hydroxy-benzoic acid methyl ester; 5-[[3-(1H-benzimidazol-2-yl)-1H-indazole-6-carbonyl]-amino]-furan-2-carboxylic acid methyl ester; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-
- 30 carboxylic acid (3-hydroxy-4-methoxy-phenyl)-amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (5-hydroxy-1H-pyrazol-3-yl)-amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (1H-pyrazol-3-yl)-amide; [3-(1H-benzimidazol-2-yl)-1H-indazol-6-yl]-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (9H-purin-6-yl)-amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid dimethylamide; [3-(1H-
- 35 benzimidazol-2-yl)-1H-indazol-6-yl]-morpholin-4-yl-methanone; 3-(1H-benzimidazol-2-yl)-1H-

- indazole-6-carboxylic acid pyrazin-2-ylamide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid cyclohexylamide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (1H-indazol-5-yl)-amide; [3-(1H-benzimidazol-2-yl)-1H-indazol-6-yl]-pyrrolidin-1-yl-methanone; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (1H-indazol-5-yl)-amide; [3-(1H-benzimidazol-2-yl)-1H-indazol-6-yl]-
- 5 6-yl]-[4-(furan-2-carbonyl)-piperazin-1-yl]-methanone; [3-(1H-benzimidazol-2-yl)-1H-indazol-6-yl]-[4-(methyl-piperazin-1-yl)-methanone; 1-{4-[3-(1H-benzimidazol-2-yl)-1H-indazole-6-carbonyl]-piperazin-1-yl}-ethanone; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (6-methoxy-pyridin-3-yl)-amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (3-hydroxy-phenyl)-amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid pyridin-4-ylamide; 3-(1H-
- 10 benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (2-morpholin-4-yl-ethyl)-amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (2-hydroxy-ethyl)-methyl-amide; 3-[[3-(1H-benzimidazol-2-yl)-1H-indazole-6-carbonyl]-amino]-butyric acid ethyl ester; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (3-hydroxy-propyl)-amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid phenylamide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid pyridin-3-
- 15 ylamide; 3-(6-methoxy-1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (4-hydroxy-phenyl)-amide; 3-(1H-benzimidazol-2-yl)-6-pyridin-4-yl-1H-indazole; 3-(5-chloro-1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (4-hydroxy-phenyl)-amide; 3-(5,6-dimethoxy-1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (4-hydroxy-phenyl)-amide; 3-(5-fluoro-1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (4-hydroxy-phenyl)-amide; 3-(6-trifluoromethyl-1H-benzimidazol-2-yl)-1H-
- 20 1H-indazole-6-carboxylic acid (4-hydroxy-phenyl)-amide; 3-(6-*tert*-butyl-1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (4-hydroxy-phenyl)-amide; 3-(6,7-dimethyl-1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (4-hydroxy-phenyl)-amide; 3-(5,6-dichloro-1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (4-hydroxy-phenyl)-amide; 3-(5,6-difluoro-1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (4-hydroxy-phenyl)-amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-
- 25 carboxylic acid (3-fluoro-4-hydroxy-phenyl)-amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (4-hydroxy-2,3-dimethyl-phenyl)-amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (4-hydroxy-2-methyl-phenyl)-amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid (4-hydroxy-phenyl)-amide; 3-(1H-benzimidazol-2-yl)-1H-indazole-6-carboxylic acid cyclopropylamide; 2-[6-(4-hydroxy-
- 30 2-methoxy-phenyl)-1H-indazol-3-yl]-3H-benzimidazole-5-sulfonic acid amide; 4-[3-(6-dimethylamino-1H-benzimidazol-2-yl)-1H-indazol-6-yl]-3-methoxy-phenol; 2-[6-(4-hydroxy-2-methoxy-phenyl)-1H-indazol-3-yl]-3H-benzimidazole-5-carboxylic acid methylamide; 3-methoxy-4-{3-[6-(4-methyl-piperazin-1-yl)-1H-benzimidazol-2-yl]-1H-indazol-6-yl}-phenol; 2-[6-(4-hydroxy-2-methoxy-phenyl)-1H-indazol-3-yl]-3H-benzimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-
- 35 amide; 4-[3-(1H-imidazol[4,5-*c*]pyridin-2-yl)-1H-indazol-6-yl]-3-methoxy-phenol; 3-[3-(1H-benzimidazol-2-yl)-1H-indazol-6-yl]-2-methoxy-phenol; 3-[3-(1H-benzimidazol-2-yl)-1H-indazol-6-

- yl]-phenol; 4-[3-(1H-benzimidazol-2-yl)-1H-indazol-6-yl]-3,5-dimethyl-phenol; 4-[3-(1H-benzimidazol-2-yl)-1H-indazol-6-yl]-3-phenoxy-phenol; 4-[3-(1H-benzimidazol-2-yl)-1H-indazol-6-yl]-benzene-1,3-diol; 4-[3-(1H-benzimidazol-2-yl)-1H-indazol-6-yl]-3-methoxy-phenol; 4-[3-(1H-benzimidazol-2-yl)-1H-indazol-6-yl]-2-methoxy-phenol; N-{3-[3-(1H-benzimidazol-2-yl)-1H-indazole-6-carbonyl]-phenyl}-benzamide; 6-[2-(1,5-dimethyl-1H-pyrazol-3-yl)-3H-benzimidazol-5-yl]-5-methyl-4,5-dihydro-2H-pyridazin-3-one; 5-methyl-6-[2-(1-methyl-1H-pyrazol-3-yl)-3H-benzimidazol-5-yl]-4,5-dihydro-2H-pyridazin-3-one; 8-(1,5-dimethyl-1H-pyrazol-3-yl)-7H-purine; 2-(1,5-dimethyl-1H-pyrazol-3-yl)-1H-imidazo[4,5-b]pyridine or 2-(5-methyl-1H-pyrazol-3-yl)-1H-imidazo[4,5-b]pyridine.
- 10
5. A compound according to claim 3 wherein R^1 is optionally substituted heteroaryl.
6. A compound according to claim 5 wherein R^1 is optionally substituted dihydrofuro-pyrazolyl, imidazolyl, indazolyl, indolyl, isoxazolyl, oxodihydropyridazinyl, oxodihydropyridinopyrazolyl, oxodihydropyridinyl, oxotetrahydropyrrolopyrazolyl, pyrazolyl, thiazolyl, thenopyrazolyl, tetrahydrocyclopentapyrazolyl, tetrahydroindazolyl, tetrahydropyranopyrazolyl, tetrahydropyridinopyrazolyl, tetrahydropyrrolopyrazolyl or triazolyl.
- 15
7. A compound according to claim 5 heteroaryl is optionally substituted by one or more groups selected from carboxy, cyano, halo, haloalkyl, hydroxy, nitro, R^4 , $-C(=O)R^4$, $-C(=O)NY^1Y^2$, $-C(=O)OR^4$, $-N(R^6)C(=O)R^4$, $-N(R^6)C(=O)NY^1Y^2$, $-N(R^6)C(=O)OR^4$, $-N(R^6)SO_2R^4$, $-N(R^6)SO_2NY^1Y^2$, $-NY^1Y^2$, $-OR^4$, $-OCF_2H$, $-OCF_3$, $-OC(=O)R^4$, $-OC(=O)NY^1Y^2$, $-S(O)_nR^4$ and $-S(O)_2NY^1Y^2$.
- 20
8. A compound according to claim 6 wherein dihydrofuro-pyrazolyl, imidazolyl, indazolyl, indolyl, isoxazolyl, oxodihydropyridazinyl, oxodihydropyridinopyrazolyl, oxodihydropyridinyl, oxotetrahydropyrrolopyrazolyl, pyrazolyl, thiazolyl, thenopyrazolyl, tetrahydrocyclopentapyrazolyl, tetrahydroindazolyl, tetrahydropyranopyrazolyl, tetrahydropyridinopyrazolyl, tetrahydropyrrolopyrazolyl or triazolyl is optionally substituted by one or more groups selected from carboxy, cyano, halo, haloalkyl, hydroxy, nitro, R^4 , $-C(=O)R^4$, $-C(=O)NY^1Y^2$, $-C(=O)OR^4$, $-N(R^6)C(=O)R^4$, $-N(R^6)C(=O)NY^1Y^2$, $-N(R^6)C(=O)OR^4$, $-N(R^6)SO_2R^4$, $-N(R^6)SO_2NY^1Y^2$, $-NY^1Y^2$, $-OR^4$, $-OCF_2H$, $-OCF_3$, $-OC(=O)R^4$, $-OC(=O)NY^1Y^2$, $-S(O)_nR^4$ and $-S(O)_2NY^1Y^2$.
- 30



- R⁷ is hydrogen or alkyl, and R⁸ and R⁹ are independently selected from hydrogen, carboxy, cyano, halo, haloalkyl, hydroxy, nitro, R⁴, -C(=O)R⁴, -C(=O)NY¹Y², -C(=O)OR⁴, -N(R⁶)C(=O)R⁴, -N(R⁶)C(=O)NY¹Y², -N(R⁶)C(=O)OR⁴, -N(R⁶)SO₂R⁴, -N(R⁶)SO₂NY¹Y², -NY¹Y², -OR⁴, -OC(=O)R⁴, -OC(=O)NY¹Y², -S(O)_nR⁴ and -S(O)₂NY¹Y²; or R⁸ and R⁹ together with the carbon atoms to which they are attached form (i) a 5 to 8 membered carbocyclic ring optionally substituted by one or more carbocyclic ring substituents; (ii) a phenyl ring optionally substituted by one or more aryl group substituents; (iii) a 5 or 6 membered heteroaromatic ring in which one or more of the ring members is/are nitrogen, oxygen or sulfur and which is optionally substituted by one or more groups selected from haloalkyl, hydroxy, halo, cyano, nitro, R⁴, -C(=O)NY¹Y², -N(R⁶)C(=O)R⁴, -N(R⁶)C(=O)NY¹Y², -N(R⁶)SO₂R⁴, -NY¹Y² and -OR⁵; or (iv) a 5 or 6 membered heterocyclic ring optionally substituted by alkyl or oxo, and containing a heteroatom-containing group selected from O, S, SO₂, and NY⁵; where Y⁵ is hydrogen, R⁴, -C(=O)R⁴, -C(=O)NY¹Y², -C(=O)OR⁴ or -SO₂R⁴.
- 15 10. A compound according to any one of claims 3 to 9 wherein W is CH; X is CR²; Y is CH or CR³; and Z is CH or CR³.
11. A compound according to any one of claims 3 to 9 wherein W is CH; when X is N; Y is CH or CR³; and Z is CH or CR³.
12. A compound according to any one of claims 3 to 9 wherein W is N; X is CH or CR²; Y is CH or CR³; and Z is CH or CR³.
- 20 13. A compound according to any one of claims 3 to 9 wherein W is N; X is CH or CR²; Y is CH or CR³; and Z is N.
14. A compound according to claim 3 of formula (Ixa)



25

wherein

R⁷ is hydrogen or alkyl;

R⁸ and R⁹ are independently selected from hydrogen, carboxy, cyano, halo, haloalkyl, hydroxy, nitro,

R⁴, -C(=O)R⁴, -C(=O)NY¹Y², -C(=O)OR⁴, -N(R⁶)C(=O)R⁴, -N(R⁶)C(=O)NY¹Y²,

-N(R⁶)C(=O)OR⁴, -N(R⁶)SO₂R⁴, -NY¹Y², -OR⁴, -OC(=O)R⁴, -OC(=O)NY¹Y², -S(O)_nR⁴ and
















5 -S(O)₂NY¹Y²; or

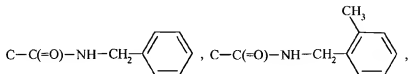
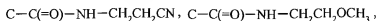
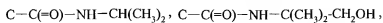
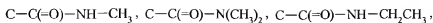
an N-oxide, prodrug, acid bisoistere, pharmaceutically acceptable salt or solvate of such compound;
or an N-oxide, prodrug, or acid bisoistere of such salt or solvate.

15. A compound according to claim 14 wherein W is CH; X is CH, Y is CH; and Z is CH or C-CH₃.

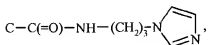
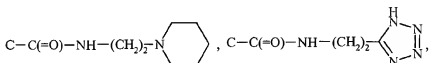
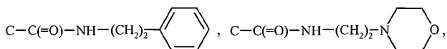
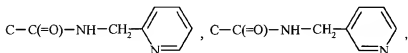
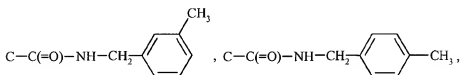
16. A compound according to claim 14 wherein W represents CH; X represents CH; Z represents CH; and Y represents C-C₁₋₄alkyl; C-aryl; C-CN; C-NO₂; C-halo; C-haloalkyl; C-heteroaryl; C-OR⁴; C-C(=O)R⁴; C-C(=O)NY¹Y²; C-C(=O)OR⁴; C-NHC(=O)R⁴; C-CH(OH)aryl; C-S(O)₂NY¹Y²; or
15 C-S(O)_nR⁴.

17. A compound according to claim 16 wherein Y represents

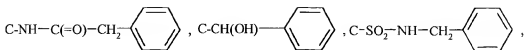
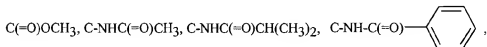
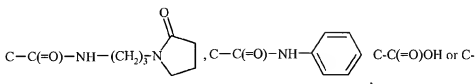
C-CH₃, C-CH₂CH₃, C-CH₂CH₂CH₃, C-CH(CH₃)₂, C-, C-,
, C-, C-, C-,
C-, C- or C-, C-CN; C-NO₂, C-Br, C-Cl, C-F;
C-CF₃, C-, C-, C-OCH₃, C-OCH₂CH₃, C-OCHF₂, C-OCF₃,
C-O-, C-O-CH₂-, C-O-(CH₂)₂-N--O; C-C(=O)-,



5




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


15

18. A compound according to claim 14 wherein

W represents CH; X represents C-CH₃, C-CH₂CH₃, C-CH(CH₃)₂, C-OCH₃, C-OCH₂CH₃,

C-Br or C-Cl; Y represents C-CH₃, C-CH₂CH₃, C-OCH₃, C-Br, C-Cl, C-F, C-

or C-C(=O)-NH-CH₂-; and Z represents CH.

19. A compound according to claim 14 wherein W represents CH; X represents CH; Y represents C-CH₃; and Z represents C-CH₃.

20. A compound according to claim 14 wherein W represents CH; X represents CR²; and Y represents CR³, where R² and R³ form the group -CH₂-O-CH₂; and Z represents CH.

10


21. A compound according to claim 14 wherein W represents CH; X represents CR²; Y represents CR³, where R² and R³ form the group -CH₂-CH₂-CH₂-; and Z represents CH.




22. A compound according to claim 14 wherein R⁷ represents hydrogen.




15

23. A compound according to claim 14 wherein R⁸ represents hydrogen, C₁₋₄alkyl, -SR⁴, -NY¹Y² or -OR⁵.

24. A compound according to claim 14 wherein R⁸ represents hydrogen, CH₃, CH₂CH₃,

20 CH(CH₃)₂ or CH(CH₃)CH₂CH₃; -S-CH₃, -S-CH₂CH₃ or -S-CH₂-,















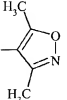


-S-CH₂-, -S-CH₂--OCH₃, -S-CH₂-CH₂-,

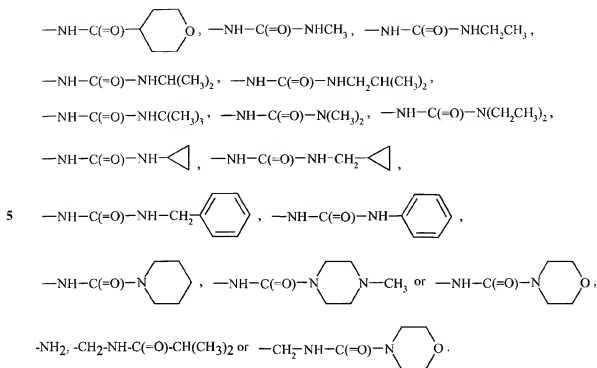
-S-CH₂- or -S-CH₂-, -N-, or -OCH₂CH₃.

25. A compound according to claim 14 wherein R⁹ represents hydrogen, C₁₋₇alkyl, aryl,

25 -C(=O)NY¹Y², -N(R⁶)C(=O)R⁴, where R⁴ is alkyl optionally substituted by aryl, cycloalkyl,

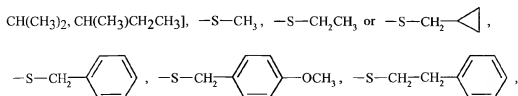
heteroaryl, heterocycloalkyl, or where R^4 is NY^1Y^2 or $-OR^5$, or where R^4 is aryl, or where R^4 is cycloalkyl, or where R^4 is heteroaryl, or where R^4 is heterocycloalkyl; or R^9 represents $-N(R^6)C(=O)NY^1Y^2$, $-NY^1Y^2$, or alkyl substituted by $-N(R^6)C(=O)NY^1Y^2$.

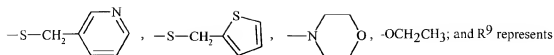
- 5 26. A compound according to claim 14 wherein R^9 represents hydrogen, $-CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2-CH_2-CH(CH_3)_2$, phenyl, $-C(=O)-NH-CH_2CH_3$, $-C(=O)-NH-CH_2CH_2CH_3$, $-C(=O)-NH-CH_2CH(CH_3)_2$, $-C(=O)-NH-CH(CH_3)_2$, $-C(=O)-NH-C(CH_3)_3$, $-C(=O)-NH-C(CH_3)_2CH_2OH$, $-C(=O)-NH-CH_2CH_2OCH_3$, $-C(=O)-N(CH_3)_2$, $-C(=O)-N(CH_2CH_3)_2$,
- 10 $-C(=O)-NH-$ , $-C(=O)-NH-CH_2-$ , $-C(=O)-NH-$ , $-NH-C(=O)-CH_3$, $-NH-C(=O)-(CH_2)_2CH_3$, $-NH-C(=O)-CH(CH_3)_2$, $-NH-C(=O)-C(CH_3)_3$, $-NH-C(=O)-CH_2CH(CH_3)_2$, $-NH-C(=O)-CH(CH_3)CH_2CH_3$, $-NH-C(=O)-CH_2C(CH_3)_3$, $-NH-C(=O)-CH_2-$ , $-NH-C(=O)-CH_2-$ , $-NH-C(=O)-CH_2-N$ , $-NH-C(=O)-CH_2-N(CH_3)_2$,
- 15 $-NH-C(=O)-CH_2-N$ , $-NH-C(=O)-CH_2-N$ , $-NH-C(=O)-CH_2OCH_3$], $-NH-C(=O)-$ , $-NH-C(=O)-$ , or $-NH-C(=O)-$ , $-NH-C(=O)-$ , or $-NH-C(=O)-$ , $-NH-C(=O)-$ , $-NH-C(=O)-$ , $-NH-C(=O)-$ , $-NH-C(=O)-$ ,



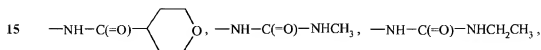
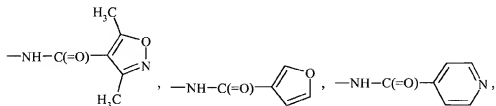
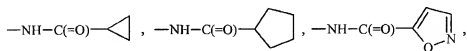
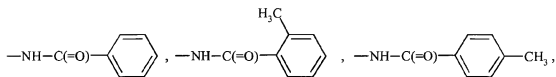
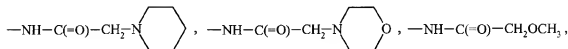
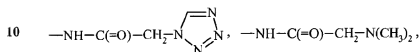
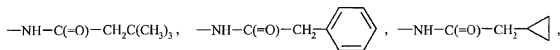
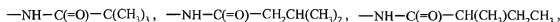
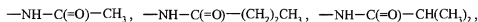
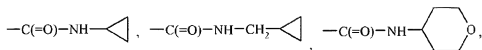
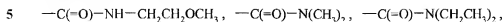
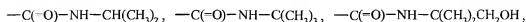
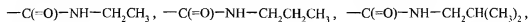
27. A compound according to claim 14 wherein
 10 W represents CH;
 X represents CH;
 Y represents CH;
 Z represents CH or C-CH₃;
 R⁷ represents hydrogen;
 15 R⁸ represents hydrogen, C₁₋₄alkyl, -SR⁴, -NY¹Y²; and
 R⁹ represents hydrogen, C₁₋₇alkyl, aryl, -C(=O)NY¹Y², -N(R⁶)C(=O)R⁴, particularly -
 NHC(=O)R⁴, -N(R⁶)C(=O)NY¹Y², -NY¹Y², or alkyl substituted by -N(R⁶)C(=O)NY¹Y².

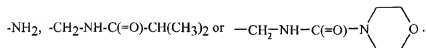
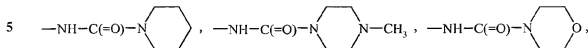
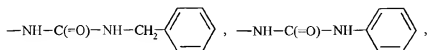
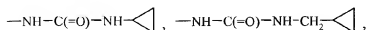
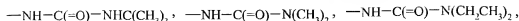
28. A compound according to claim 14 wherein W represents CH; X represents CH; Y represents
 20 CH; Z represents CH or C-CH₃; R⁷ represents hydrogen; R⁸ represents hydrogen, CH₃, CH₂CH₃,





hydrogen, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, phenyl,





29. A compound according to claim 14 wherein

W represents CH;

10 X represents CH;

Z represents CH;

Y represents C-C₁₋₄alkyl, C-aryl, C-CN, C-NO₂, C-halo, C-haloalkyl, C-heteroaryl, C-OR⁴,

C-C(=O)R⁴, C-C(=O)NY¹Y², C-C(=O)OR⁴, or C-CH(OH)aryl;

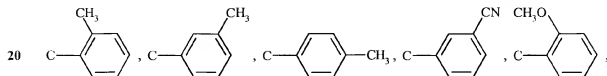
R⁸ represents hydrogen, C₁₋₄alkyl, -SR⁴, -NY¹Y² or -OR⁵; and

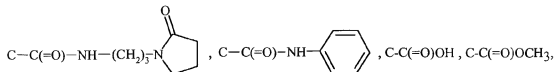
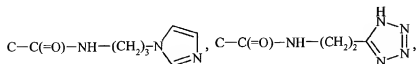
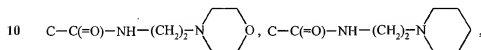
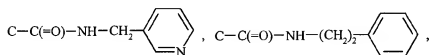
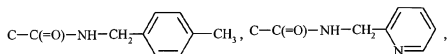
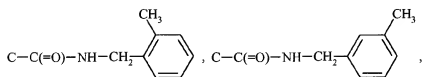
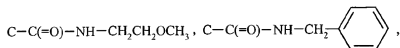
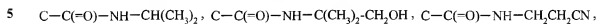
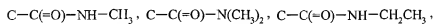
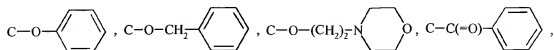
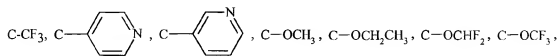
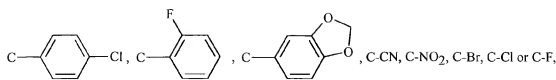
15 R⁹ represents hydrogen, C₁₋₇alkyl, aryl, -C(=O)NY¹Y², -N(R⁶)C(=O)R⁴,

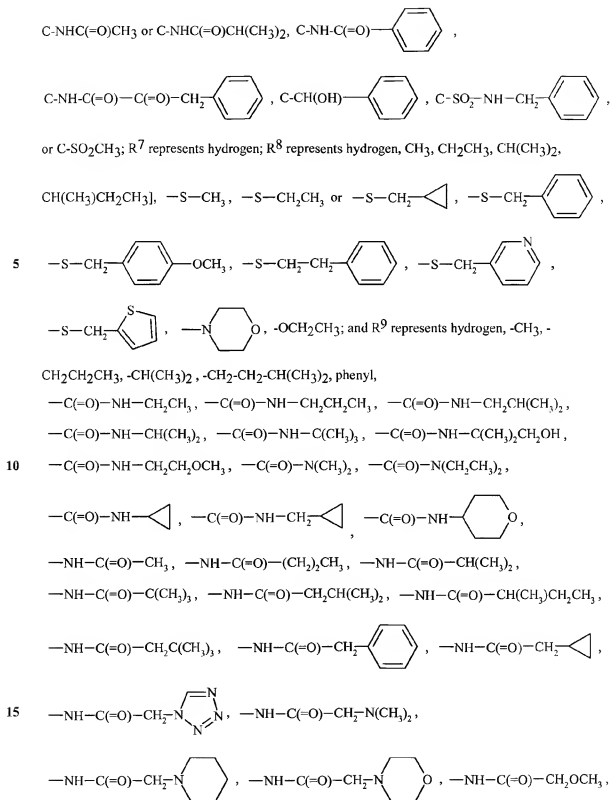
-N(R⁶)C(=O)NY¹Y², -NY¹Y², or alkyl substituted by -N(R⁶)C(=O)NY¹Y².

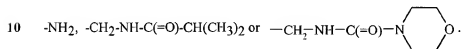
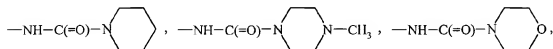
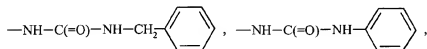
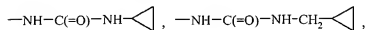
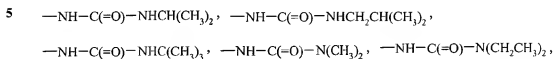
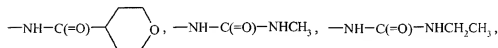
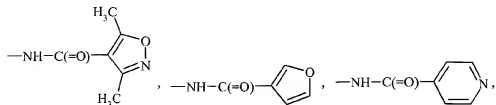
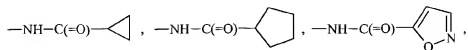
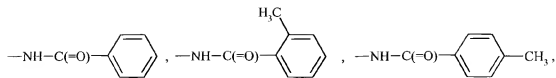
30. A compound according to claim 14 wherein W represents CH; X represents CH; Z represents

CH; Y represents C-CH₃, C-CH₂CH₃, C-CH₂CH₂CH₃, C-CH(CH₃)₂, C-C₆H₅,








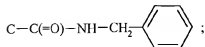


31. A compound according to claim 14 wherein

W represents CH_3 ;

X represents $\text{C}-\text{CH}_3, \text{C}-\text{CH}_2\text{CH}_3, \text{C}-\text{CH}(\text{CH}_3)_2, \text{C}-\text{OCH}_3, \text{C}-\text{OCH}_2\text{CH}_3, \text{C}-\text{Br}$ or $\text{C}-\text{Cl}$;

Y represents C-CH₃, C-CH₂CH₃, C-OCH₃, C-Br, C-Cl, C-F, C- or



Z represents CH;



5 R⁷ represents hydrogen;

R⁸ represents hydrogen, C₁₋₄alkyl, -SR⁴, -NY¹Y², or -OR⁵; and

R⁹ represents hydrogen, C₁₋₇alkyl, aryl, -C(=O)NY¹Y², -N(R⁶)C(=O)R⁴,
-N(R⁶)C(=O)NY¹Y², -NY¹Y², or alkyl substituted by -N(R⁶)C(=O)NY¹Y².



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


32. A compound according to claim 14 wherein W represents CH; X represents C-CH₃, C-CH₂CH₃, C-CH(CH₃)₂, C-OCH₃, C-OCH₂CH₃, C-Br or C-Cl; Y represents C-CH₃, C-CH₂CH₃,



C-OCH₃, C-Br, C-Cl, C-F, C- or C-C(=O)-NH-CH₂-; Z represents CH;

R⁷ represents hydrogen; R⁸ represents hydrogen, CH₃, CH₂CH₃, CH(CH₃)₂, CH(CH₃)CH₂CH₃],

15

-S-CH₃, -S-CH₂CH₃ or -S-CH₂-, -S-CH₂-,

-S-CH₂--OCH₃, -S-CH₂-CH₂-, -S-CH₂-,

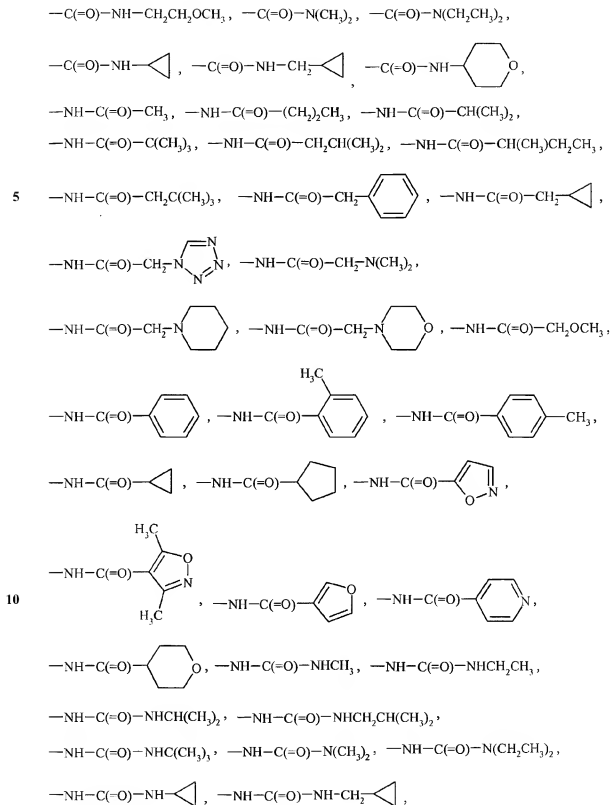
-S-CH₂-, -N<O, -OCH₂CH₃; and R⁹ represents hydrogen, -CH₃, -

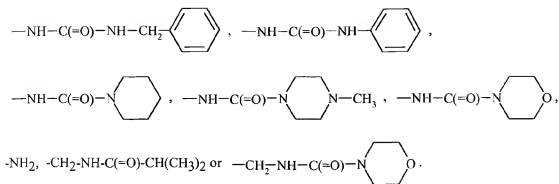
CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂-CH₂-CH(CH₃)₂, phenyl,







-C(=O)-NH-CH₂CH₃, -C(=O)-NH-CH₂CH₂CH₃, -C(=O)-NH-CH₂CH(CH₃)₂,

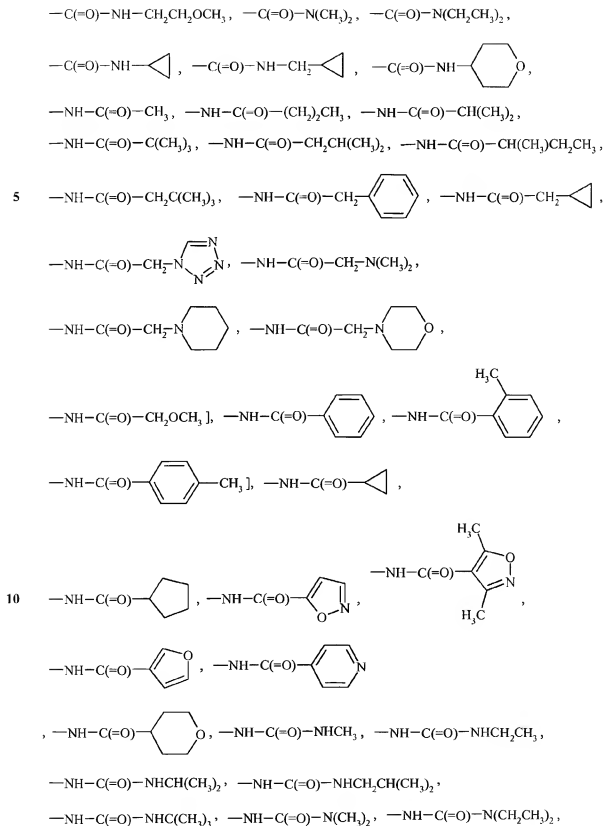
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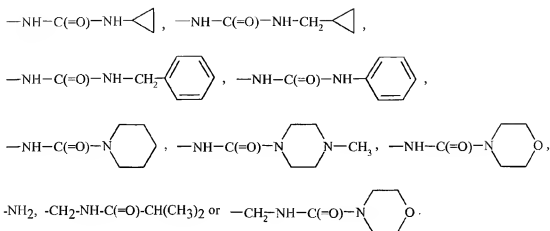
-C(=O)-NH-CH(CH₃)₂, -C(=O)-NH-C(CH₃)₃, -C(=O)-NH-C(CH₃)₂CH₂OH,



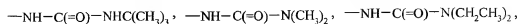
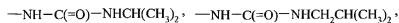
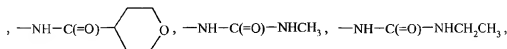
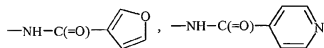
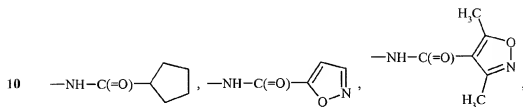
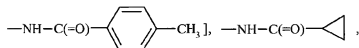
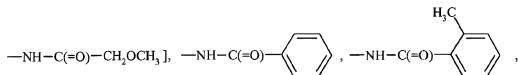
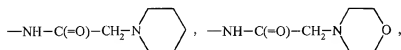
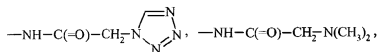
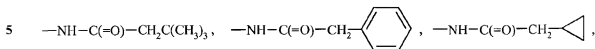
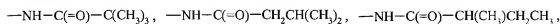
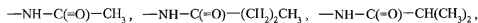
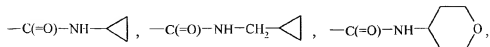
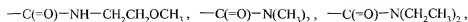


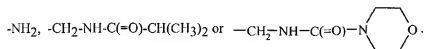
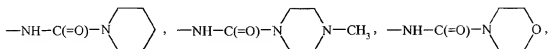
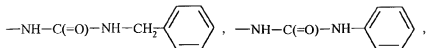
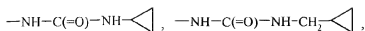
- 5 33. A compound according to claim 14 wherein
 W represents CH;
 X represents CH;
 Y represents C-CH₃;
 Z represents C-CH₃;
 10 R⁷ represents hydrogen;
 R⁸ represents hydrogen, C₁₋₄alkyl, -SR⁴, -NY¹Y², or -OR⁵; and
 R⁹ represents hydrogen, C₁₋₇alkyl, aryl, -C(=O)NY¹Y²; -N(R⁶)C(=O)R⁴,
 -N(R⁶)C(=O)NY¹Y², -NY¹Y², or alkyl substituted by -N(R⁶)C(=O)NY¹Y².
 15 34. A compound according to claim 14 wherein W represents CH; X represents CH; Y
 represents C-CH₃; Z represents C-CH₃; R⁷ represents hydrogen; R⁸ represents hydrogen, CH₃,
 CH₂CH₃, CH(CH₃)₂, CH(CH₃)CH₂CH₃, -S-CH₃, -S-CH₂CH₃ or -S-CH₂-,
 -S-CH₂-, -S-CH₂--OCH₃, -S-CH₂-CH₂-,
 -S-CH₂-, -S-CH₂-J, -N-C₆H₁₁O, -OCH₂CH₃; and R⁹ represents
 20 hydrogen, -CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂-CH₂-CH(CH₃)₂,
 phenyl, -C(=O)-NH-CH₂CH₂CH₃, -C(=O)-NH-CH₂CH₂(CH₃)₂,
 -C(=O)-NH-CH(CH₃)₂, -C(=O)-NH-C(CH₃)₃, -C(=O)-NH-C(CH₃)₂CH₂OH,





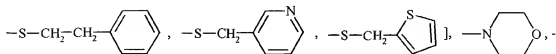
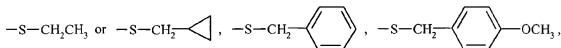
- 5 35. A compound according to claim 14 wherein
 W represents CH_3 ;
 X represents CR^2 and Y represents CR^3 where R^2 and R^3 form the group $-\text{CH}_2-\text{O}-\text{CH}_2-$;
 Z represents CH_3 ;
 R^7 represents hydrogen;
 10 R^8 represents hydrogen, $\text{C}_{1-4}\text{alkyl}$, $-\text{SR}^4$, $-\text{NY}^1\text{Y}^2$, or $-\text{OR}^5$; and
 R^9 represents hydrogen, $\text{C}_{1-7}\text{alkyl}$, aryl, $-\text{C}(=\text{O})\text{NY}^1\text{Y}^2$; $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{R}^4$,
 $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{NY}^1\text{Y}^2$, $-\text{NY}^1\text{Y}^2$, or alkyl substituted by $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{NY}^1\text{Y}^2$.
36. A compound according to claim 14 wherein W represents CH_3 ; X represents CR^2 and Y
 15 represents CR^3 where R^2 and R^3 form the group $-\text{CH}_2-\text{O}-\text{CH}_2-$; Z represents CH_3 ; R^7 represents
 hydrogen; R^8 represents hydrogen, CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $-\text{S}-\text{CH}_3$,
 $-\text{S}-\text{CH}_2\text{CH}_3$ or $-\text{S}-\text{CH}_2-\triangle$, $-\text{S}-\text{CH}_2-\text{C}_6\text{H}_5$, $-\text{S}-\text{CH}_2-\text{C}_6\text{H}_4-\text{OCH}_3$,
 $-\text{S}-\text{CH}_2-\text{CH}_2-\text{C}_6\text{H}_5$, $-\text{S}-\text{CH}_2-\text{C}_5\text{H}_4\text{N}$, $-\text{S}-\text{CH}_2-\text{C}_4\text{H}_3\text{S}$, $-\text{N}(\text{C}_6\text{H}_{11})\text{O}$,
 OCH_2CH_3 ; and R^9 represents hydrogen, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)_2$,
 20 phenyl, $-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}(\text{CH}_3)_2$,
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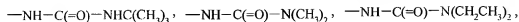
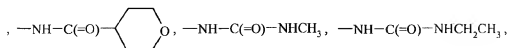
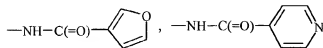
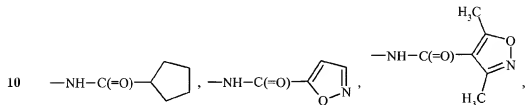
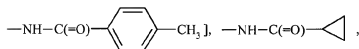
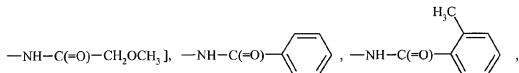
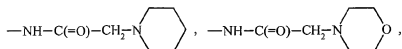
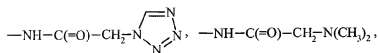
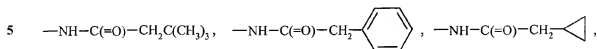
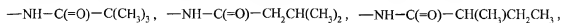
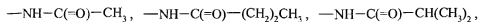
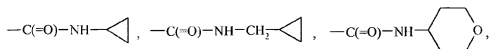
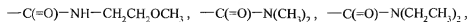


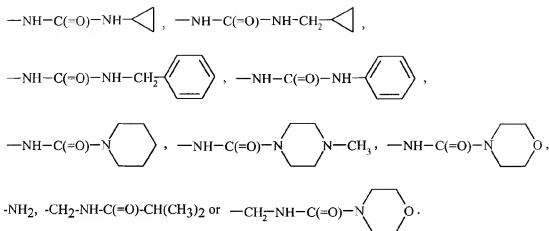
- 5 37. A compound according to claim 14 wherein
W represents CH;
X represents CR² and Y represents CR³ where R² and R³ form the group -CH₂-CH₂-CH₂;
Z represents CH;
R⁷ represents hydrogen;
10 R⁸ represents hydrogen, C₁₋₄alkyl, -SR⁴, -NY¹Y², or -OR⁵; and
R⁹ represents hydrogen, C₁₋₇alkyl, aryl, -C(=O)NY¹Y², -N(R⁶)C(=O)R⁴,
-N(R⁶)C(=O)NY¹Y², -NY¹Y² or alkyl substituted by -N(R⁶)C(=O)NY¹Y².

38. A compound according to claim 14 wherein W represents CH; X represents CR² and Y
15 represents CR³ where R² and R³ form the group -CH₂-CH₂-CH₂-; Z represents CH; R⁷ represents
hydrogen; R⁸ represents hydrogen, CH₃, CH₂CH₃, CH(CH₃)₂, CH(CH₃)CH₂CH₃, -S-CH₃,



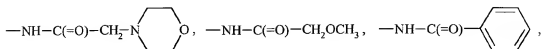
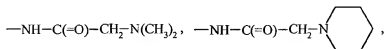
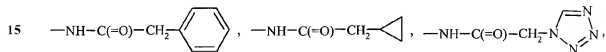
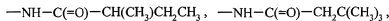
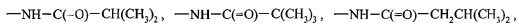
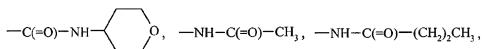
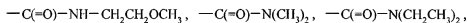
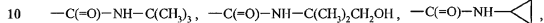
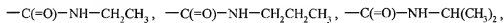
- OCH₂CH₃; and R⁹ represents hydrogen, -CH₃, -CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂-CH₂-CH(CH₃)₂,
20 phenyl, -C(=O)-NH-CH₂CH₂CH₃, -C(=O)-NH-CH₂CH(CH₃)₂,
-C(=O)-NH-CH(CH₃)₂, -C(=O)-NH-C(CH₃)₃, -C(=O)-NH-C(CH₃)₂CH₂OH,

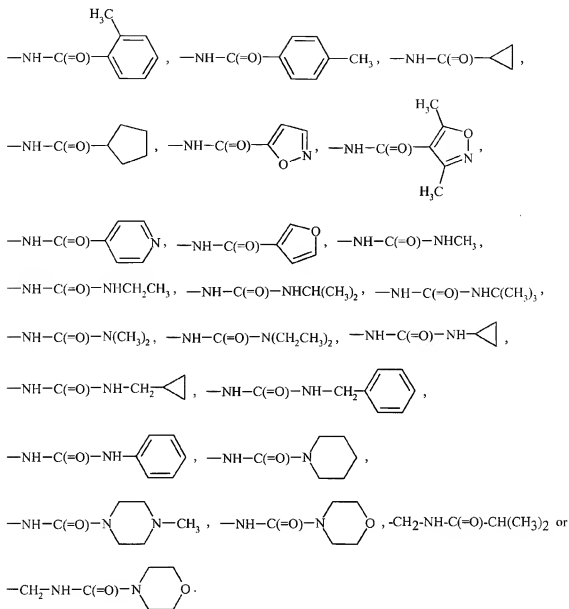




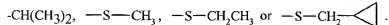
5

39. A compound according to claim 14 wherein

 R^8 is hydrogen or $-\text{CH}_3$; and R^9 is $-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)_2$,



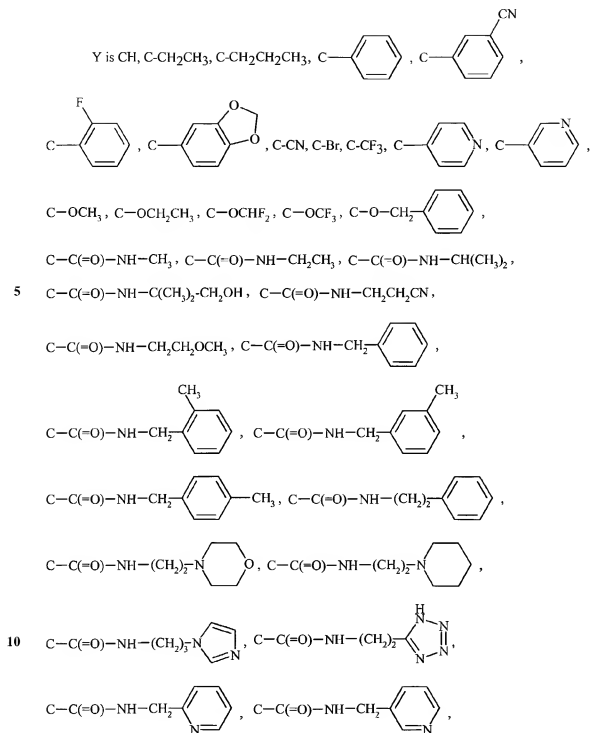
10 40. A compound according to claim 14 wherein R^9 represents hydrogen and R^8 represents

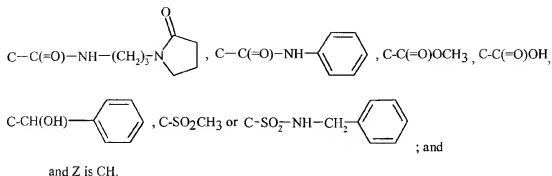


41. A compound according to claim 14 wherein

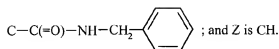
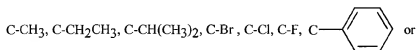
W is CH;

15 X is CH;





- 5 42. A compound according to claim 14 wherein W is CH; X is C-CH₃ or C-CH₂CH₃; Y is



43. A compound according to claim 14 wherein W is CH; X is C-OCH₃; Y is CH, C-CH₃,
 10 C-CH₂CH₃, C-Cl or C-OCH₃; and Z is CH.

44. A compound according to claim 14 wherein W is CH; X is C-OCH₂CH₃; Y is C-F; and
 Z is CH.

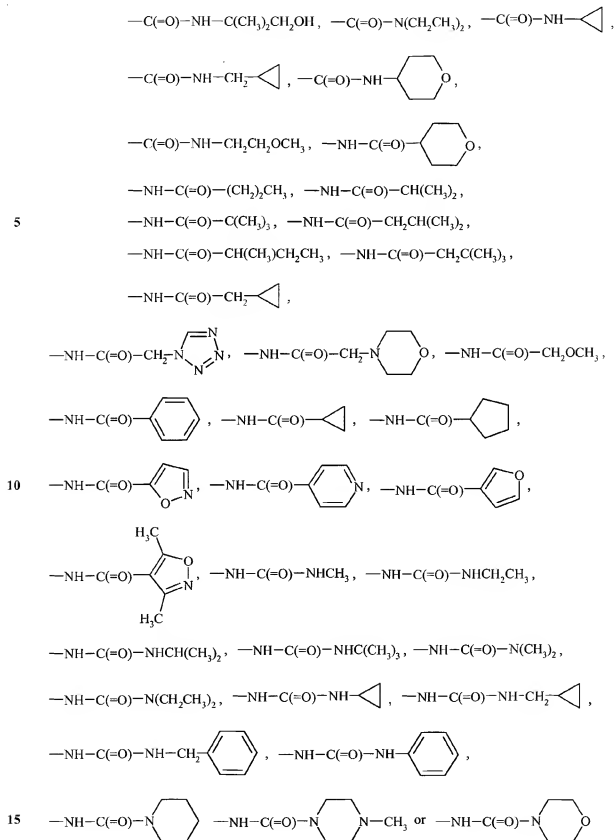
- 15 45. A compound according to claim 14 wherein W represents CH; X represents CR² and Y
 represents CR³ where R² and R³ atoms form the group -CH₂-CH₂-CH₂-; and Z represents CH.

46. A compound according to claim 14 wherein W represents CH; X represents CR² and Y
 represents CR³ where R² and R³ form the group -CH₂-O-CH₂-; and Z represents CH.

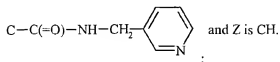
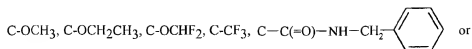
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47. A compound according to claim 14 wherein R⁸ is hydrogen or -CH₃; and
 R⁹ is $-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_3$,

48. $-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{C}(=\text{O})-\text{NH}-\text{CH}(\text{CH}_3)_2$,
 $-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{C}(=\text{O})-\text{NH}-\text{C}(\text{CH}_3)_3$,



48. W is CH; X is CH; Y is



5

49. A compound according to claim 14 wherein W is CH; X is C-CH_3 or $\text{C-CH}_2\text{CH}_3$; Y is C-CH_3 or $\text{C-CH}_2\text{CH}_3$, C-Cl or C-F ; and Z is CH.

10

50. A compound according to claim 14 wherein W is CH; X is C-OCH_3 ; Y is C-CH_3 , $\text{C-CH}_2\text{CH}_3$, C-Cl , C-F , or C-OCH_3 ; and Z is CH.

51. A compound according to claim 14 wherein W is CH; X is $\text{C-OCH}_2\text{CH}_3$; Y is C-Cl or C-F ; and Z is CH.

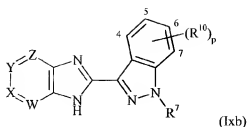
15

52. A compound according to claim 14 wherein W represents CH; X represents CR^2 and Y represents CR^3 where R^2 and R^3 form the group $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$; and Z represents CH.

20

53. A compound according to claim 14 wherein W represents CH; X represents CR^2 and Y represents CR^3 where R^2 and R^3 form the group $-\text{CH}_2-\text{O}-\text{CH}_2-$; and Z represents CH.

54. A compound according to claim 3 of the formula (Ixb)



wherein

R^7 is hydrogen or alkyl;

R^{10} is carboxy, cyano, halo, haloalkyl, hydroxy, nitro, R^4 , $-C(=O)R^4$, $-C(=O)NY^1Y^2$, $-C(=O)OR^4$,

- 5 $-N(R^6)C(=O)R^4$, $-N(R^6)C(=O)NY^1Y^2$, $-N(R^6)C(=O)OR^4$, $-N(R^6)SO_2R^4$, $-N(R^6)SO_2NY^1Y^2$, $-NY^1Y^2$, $-OR^4$, $-OCF_2H$, $-OCF_3$, $-OC(=O)R^4$, $-OC(=O)NY^1Y^2$, $-S(O)_nR^4$ or $-S(O)_2NY^1Y^2$;

and p is zero, or an integer 1;

or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.

10

55. A compound according to claim 54 wherein

W represents CH; X represents CH; Y represents CH; and Z represents CH or $C-CH_3$.

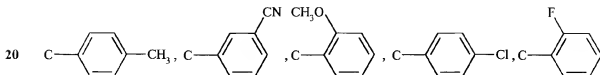
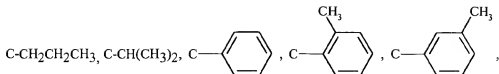
56. A compound according to claim 54 wherein

W represents CH; X represents CH; Z represents CH; and Y represents $C-C_{1-4}alkyl$, C-aryl, C-CN, C-NO₂, C-halo, C-haloalkyl, C-heteroaryl, C-OR⁴, $C-C(=O)R^4$, $C-C(=O)NY^1Y^2$,

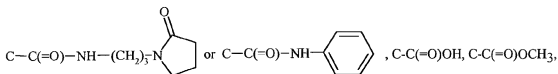
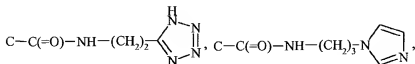
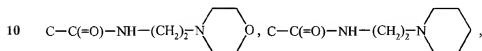
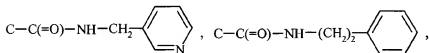
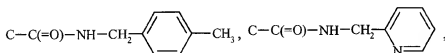
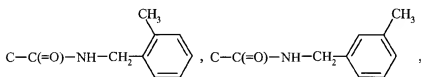
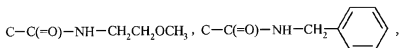
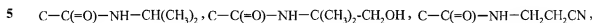
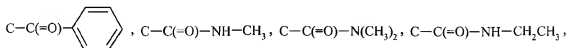
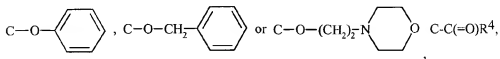
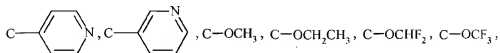
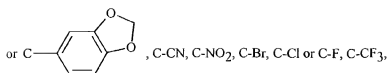
- 15 $C-C(=O)OR^4$, C-NHC(=O)R⁴, C-CH(OH)aryl, C-S(O)₂NY¹Y², or C-S(O)_nR⁴.

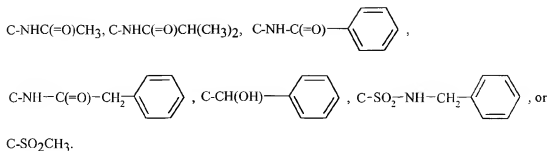
57. A compound according to claim 54 wherein



W represents CH; X represents CH; Z represents CH; and Y represents C-CH₃, C-CH₂CH₃,



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- 5 58. A compound according to claim 54 wherein W represents CH; X represents C-CH_3 , $\text{C-CH}_2\text{CH}_3$, $\text{C-CH(CH}_3)_2$, C-OCH_3 , $\text{C-OCH}_2\text{CH}_3$, C-Br or C-Cl ; Y represents C-CH_3 , $\text{C-CH}_2\text{CH}_3$, C-OCH_3 , C-Br , C-Cl , C-F , C-  or C-C(=O)-NH-CH_2-  and Z represents CH.

- 10 59. A compound according to claim 54 wherein W represents CH; X represents CH; Y represents C-CH_3 ; and Z represents C-CH_3 .

60. A compound according to claim 54 wherein W represents CH; X represents CR^2 and Y represents CR^3 where R^2 and R^3 form the group $-\text{CH}_2\text{-O-CH}_2-$; and Z represents CH.
















- 15 61. A compound according to claim 54 wherein W represents CH; X represents CR^2 and Y represents CR^3 where R^2 and R^3 form the group $-\text{CH}_2\text{-CH}_2\text{-CH}_2-$; and Z represents CH.

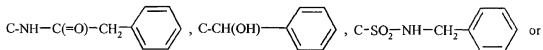
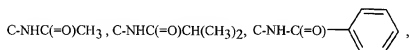
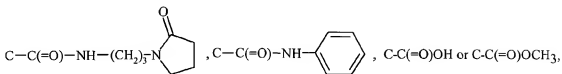
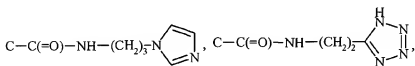
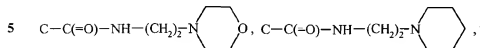
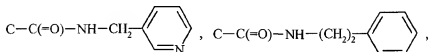
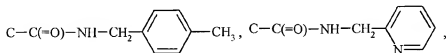
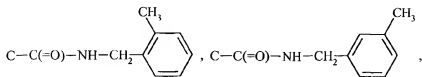
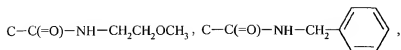
62. A compound according to claim 54 wherein R^7 represents hydrogen.

- 20 63. A compound according to claim 54 wherein p is zero or one.

64. A compound according to claim 54 wherein R^{10} represents cyano, halo, C_{1-4} alkyl, $-\text{OR}^4$, or $-\text{C(=O)NY}^1\text{Y}^2$.

- 25 65. A compound according to claim 54 wherein R^{10} represents cyano, chloro, fluoro, methyl, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C(=O)-NH}_2$, $-\text{C(=O)-NHCH(CH}_3)_2$, or $-\text{C(=O)-N(CH}_3)_2$.

66. A compound according to claim 54 wherein W represents CH; X represents CH; Y represents CH; Z represents CH or C-CH₃; R⁷ represents hydrogen; and R¹⁰ represents cyano, halo, C₁₋₄alkyl, -OR⁴ or -C(=O)NY¹Y².
67. A compound according to claim 54 wherein W represents CH; X represents CH; Y represents CH; Z represents CH or C-CH₃; R⁷ represents hydrogen; and R¹⁰ represents cyano, chloro, fluoro, methyl, -OCH₃ or -OCH₂CH₃, -C(=O)-NH₂, -C(=O)-NHCH(CH₃)₂ or -C(=O)-N(CH₃)₂.
68. A compound according to claim 54 wherein W represents CH; X represents CH; Z represents CH; Y represents C-C₁₋₄alkyl, C-aryl, C-CN, C-NO₂, C-halo, C-haloalkyl, C-OR⁴, C-C(=O)R⁴, C-C(=O)NY¹Y², -C(=O)OR⁴, C-NHC(=O)R⁴, C-S(O)₂NY¹Y², or C-S(O)_nR⁴; R⁷ represents hydrogen; p is zero or one; and R¹⁰ represents cyano, halo, C₁₋₄alkyl, -OR⁴, -C(=O)NY¹Y².
69. A compound according to claim 54 wherein W represents CH; X represents CH; Z represents CH; Y represents C-CH₃, C-CH₂CH₂CH₃, C-CH₂CH₂CH₃, C-CH(CH₃)₂, C-, , , , , , , , , C-CN, C-NO₂, C-Br, C-Cl, C-F, C-CF₃, C-, C-, C-OCH₃, C-OCH₂CH₃, C-OCHF₂, C-OCF₃, C-O-, C-O-CH₂-, C-O-(CH₂)₂-N-, C-C(=O)-, C-C(=O)-NH-CH₃, C-C(=O)-N(CH₃)₂, C-C(=O)-NH-CH₂CH₃, C-C(=O)-NH-CH(CH₃)₂, C-C(=O)-NH-C(CH₃)₂-CH₂OH, C-C(=O)-NH-CH₂CH₂CN,



- 10 $\text{C}-\text{SO}_2\text{CH}_3$; R^7 represents hydrogen; p is zero or one; R^{10} represents cyano, chloro, fluoro, methyl, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(=\text{O})-\text{NH}_2$, $-\text{C}(=\text{O})-\text{NHCH}(\text{CH}_3)_2$ or $-\text{C}(=\text{O})-\text{N}(\text{CH}_3)_2$.



70. A compound according to claim 54 wherein W represents CH_3 ; X represents $\text{C}-\text{CH}_3$, $\text{C}-\text{CH}_2\text{CH}_3$, $\text{C}-\text{CH}(\text{CH}_3)_2$, $\text{C}-\text{OCH}_3$, $\text{C}-\text{OCH}_2\text{CH}_3$, $\text{C}-\text{Br}$ or $\text{C}-\text{Cl}$; Y represents $\text{C}-\text{CH}_3$, $\text{C}-\text{CH}_2\text{CH}_3$,

- 15 $\text{C}-\text{OCH}_3$, $\text{C}-\text{Br}$, $\text{C}-\text{Cl}$, $\text{C}-\text{F}$, $\text{C}-\text{C}_6\text{H}_5$ or $\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}_2-\text{C}_6\text{H}_5$; Z represents CH_3 ;

R^7 represents hydrogen; p is zero or one; and R^{10} represents cyano, halo, C_{1-4} alkyl, OR^4 , or $-C(=O)NY^1Y^2$.

71. A compound according to claim 54 wherein W represents CH; X represents C-CH₃,

5 C-CH₂CH₃, C-CH(CH₃)₂, C-OCH₃, C-OCH₂CH₃, C-Br or C-Cl; Y represents C-CH₃, C-CH₂CH₃,

C-OCH₃, C-Br, C-Cl, C-F, C- or C-C(=O)-NH-CH₂-; Z represents CH;

R^7 represents hydrogen; p is zero or one; R^{10} represents cyano, halo, chloro, fluoro, methyl], -OCH₃, -OCH₂CH₃, -C(=O)-NH₂, -C(=O)-NHCH(CH₃)₂ or -C(=O)-N(CH₃)₂.

10 72. A compound according to claim 54 wherein W represents CH; X represents CH; Y represents C-CH₃; Z represents C-CH₃; R^7 represents hydrogen; p is zero or one; and R^{10} represents cyano, halo, C_{1-4} alkyl, -OR⁴, or -C(=O)NY¹Y².

73. A compound according to claim 54 wherein W represents CH; X represents CH; Y











15 represents C-CH₃; Z represents C-CH₃; R^7 represents hydrogen; p is zero or one; and R^{10} represents cyano, chloro, fluoro, methyl, -OCH₃, -OCH₂CH₃, -C(=O)-NH₂, -C(=O)-NHCH(CH₃)₂ or -C(=O)-N(CH₃)₂.

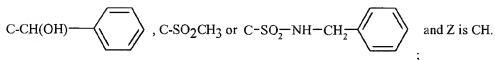
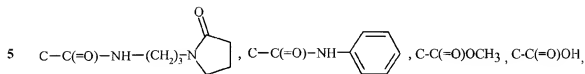
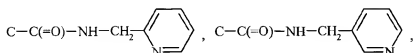
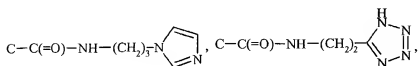
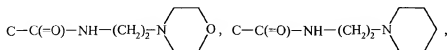
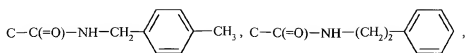
74. A compound according to claim 54 wherein W represents CH; X represents CR² and Y

20 represents CR³ where R² and R³ form the group -CH₂-O-CH₂-; Z represents CH; R^7 represents hydrogen; p is zero or one; and R^{10} represents cyano, halo, C_{1-4} alkyl, -OR⁴, or -C(=O)NY¹Y².

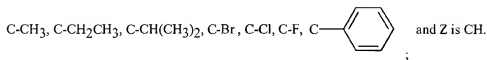
75. A compound according to claim 54 wherein W represents CH; X represents CR² and Y represents CR³ where R² and R³ form the group -CH₂-O-CH₂-; Z represents CH; R^7 represents

25 hydrogen; p is zero or one; and R^{10} represents cyano, chloro, fluoro, methyl, -OCH₃, -OCH₂CH₃, -C(=O)-NH₂, -C(=O)-NHCH(CH₃)₂ or -C(=O)-N(CH₃)₂.

76. A compound according to claim 54 wherein W represents CH; X represents CR² and Y represents CR³ where R² and R³ form the group -CH₂-CH₂-CH₂-; Z represents CH; R⁷ represents hydrogen; p is zero or one; and R¹⁰ represents cyano, halo, C1-4alkyl, -OR⁴, or -C(=O)NY¹Y².
- 5 77. A compound according to claim 54 wherein W represents CH; X represents CR² and Y represents CR³ where R² and R³ form the group -CH₂-CH₂-CH₂-; Z represents CH; R⁷ represents hydrogen; p is zero or one; and R¹⁰ represents cyano, chloro, fluoro, methyl, -OCH₃, -OCH₂CH₃, -C(=O)-NH₂, -C(=O)-NHCH(CH₃)₂ or -C(=O)-N(CH₃)₂.
- 10 78. A compound according to claim 54 wherein R⁷ represents hydrogen and p is zero.
79. A compound according to claim 54 wherein R⁷ represents hydrogen; p is one; and R¹⁰ represents cyano, chloro, fluoro, methyl, -OCH₃, -OCH₂CH₃, -C(=O)-NH₂, -C(=O)-NHCH(CH₃)₂ or -C(=O)-N(CH₃)₂.
- 15 80. A compound according to claim 54 wherein W is CH; X is CH; Y is CH, C-CH₂CH₃,
 C-CH₂CH₂CH₃, C-, C-, C-, C-,
 C-CN, C-Br, C-CF₃, C-, C-, C-OCH₃, C-OCH₂CH₃, C-OCHF₂,
 C-OCF₃, C-O-CH₂-, C-C(=O)-NH-CH₃, C-C(=O)-NH-CH₂CH₃,
 C-C(=O)-NH-CH(CH₃)₂, C-C(=O)-NH-C(CH₃)₂-CH₂OH, C-C(=O)-NH-CH₂CH₂CN,
 C-C(=O)-NH-CH₂CH₂OCH₃, C-C(=O)-NH-CH₂-,
 C-C(=O)-NH-CH₂-, C-C(=O)-NH-CH₂-,



81. A compound according to claim 54 wherein W is CH; X is C-CH₃ or C-CH₂CH₃; Y is



10

82. A compound according to claim 54 wherein W is CH; X is C-OCH₃; Y is CH, C-CH₃, C-CH₂CH₃, C-Cl or C-OCH₃; and Z is CH.

83. A compound according to claim 54 wherein W is CH; X is C-OCH₂CH₃; Y is C-F and

15 Z is CH.

84. A compound according to claim 54 wherein W represents CH; X represents CR² and Y represents CR³ where R² and R³ form the group -CH₂-CH₂-CH₂-; and Z represents CH.

85. A compound according to claim 54 wherein W represents CH; X represents CR² and Y represents CR³ where R² and R³ form the group -CH₂-O-CH₂-; and Z represents CH.

86. A compound according to claim 54 wherein R⁷ represents hydrogen and p is zero.

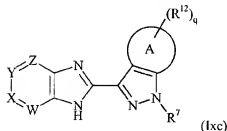
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87. A compound according to claim 54 wherein R⁷ represents hydrogen; p is one; and R¹⁰ represents -OCH₃, -OCH₂CH₃ or -C(=O)-NHCH(CH₃)₂ attached to position 5 of the indazolyl ring.

88. A compound according to claim 54 wherein W is CH; X is C-CH₃ or C-CH₂CH₃; Y is

10 C-CH₃ or C-CH₂CH₃ and Z is CH.

89. A compound according to claim 3 of the formula (Ixc)



15

wherein R⁷ is hydrogen or alkyl;



is a C₅-cycloalkyl ring; and R¹² is acyl, acylamino, alkoxy, alkoxycarbonyl, alkylenedioxy,




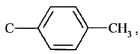
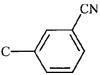

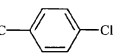

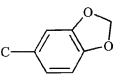






alkylsulfinyl, alkylsulfonyl, alkylthio, aroyl, aroylamino, aryl, arylalkyloxy, arylalkyloxycarbonyl, arylalkylthio, aryloxy, aryloxycarbonyl, arylsulfinyl, arylsulfonyl, arylthio, carboxy or an acid bioisostere, cyano, cycloalkyl, halo, heteroaroyl, heteroaryl, heteroarylalkyloxy, heteroaroylamino,

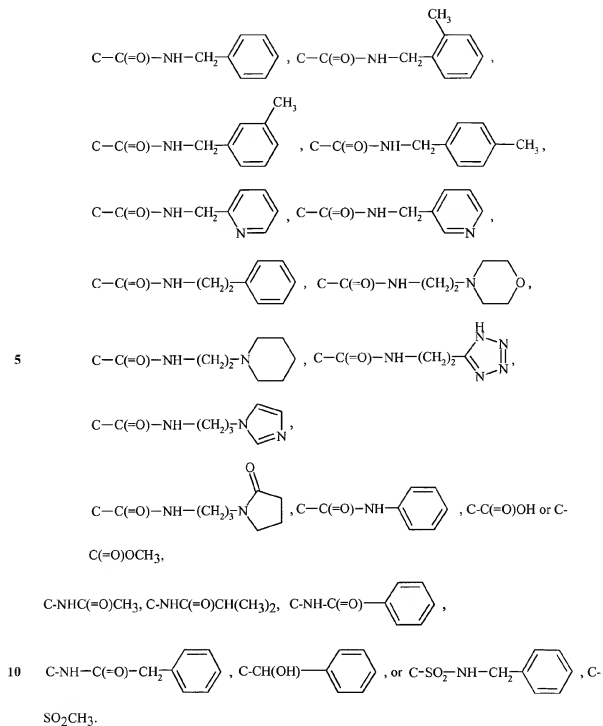
20 heteroaryloxy, heterocycloalkyl, hydroxy, nitro, trifluoromethyl, -C(=O)NY¹Y², -NY¹-C(=O)alkyl, -NY¹SO₂alkyl, -NY¹Y², -SO₂NY¹Y² or alkyl, alkenyl or alkynyl each optionally substituted with

aryl, cycloalkyl, heteroaryl, hydroxy, -C(=O)OR⁶, -C(=O)NY¹Y², -NY¹Y² or -OR⁵; or



an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.

25

90. A compound according to claim 89 wherein W represents CH; X represents CH; Y represents CH; and Z represents CH or C-CH₃.
91. A compound according to claim 89 wherein W represents CH; X represents CH; Z represents CH; and Y represents C-C₁₋₄alkyl, C-aryl, C-CN, C-NO₂, C-halo, C-haloalkyl, C-heteroaryl, C-OR⁴, C-C(=O)R⁴, C-C(=O)NY¹Y², C-C(=O)OR⁴, C-NHC(=O)R⁴, C-CH(OH)aryl, C-S(O)₂NY¹Y², or C-S(O)_nR⁴.
92. A compound according to claim 89 wherein W represents CH; X represents CH; Z represents CH; and Y represents C-CH₃, C-CH₂CH₃, C-CH₂CH₂CH₃, C-CH(CH₃)₂, C-,
- 10 C-, C-, C-,
- C-, C-, C-, C-,
- C-, C-CN, C-NO₂, C-Br, C-Cl or C-F, C-CF₃, C-,
- C-, C-OCH₃, C-OCH₂CH₃, C-OCHF₂, C-OCF₃, C-O-,
- 15 C-O-CH₂-, C-O-(CH₂)₂N-, C-C(=O)-,
- C-C(=O)-NH-CH₃, C-C(=O)-N(CH₃)₂, C-C(=O)-NH-CH₂CH₃,
- C-C(=O)-NH-CH(CH₃)₂, C-C(=O)-NH-C(CH₃)₂-CH₂OH,
- C-C(=O)-NH-CH₂CH₂CN, C-C(=O)-NH-CH₂CH₂OCH₃,





93. A compound according to claim 89 wherein W represents CH; X represents C-CH₃, C-CH₂CH₃, C-CH(CH₃)₂, C-OCH₃, C-OCH₂CH₃, C-Br or C-Cl; Y represents C-CH₃,

C-CH₂CH₃, C-OCH₃, C-Br, C-Cl, C-F, C- or C-C(=O)-NH-CH₂- and ;

Z represents CH.

94. A compound according to claim 89 wherein W represents CH; X represents C-CH₃,

5 C-CH₂CH₃, C-CH(CH₃)₂, C-OCH₃, C-OCH₂CH₃, C-Br or C-Cl; Y represents C-CH₃, C-CH₂CH₃,


C-OCH₃, C-Br, C-Cl, C-F, C- or C-C(=O)-NH-CH₂- and Z represents CH.


95. A compound according to claim 89 wherein W represents CH; X represents CR² and Y

10 represents CR³ where R² and R³ form the group -CH₂-O-CH₂-; and Z represents CH.

96. A compound according to claim 89 wherein W represents CH; X represents CR² and Y represents CR³ where R² and R³ form the group -CH₂-CH₂-CH₂-; and Z represents CH.


15 97. A compound according to claim 89 wherein R⁷ represents hydrogen.


98. A compound according to claim 89 wherein  represents a cyclopentyl, cyclohexyl or cycloheptyl ring.

20 99. A compound according to claim 89 wherein  represents a cyclohexyl ring.

















100. A compound according to claim 89 wherein q is zero.

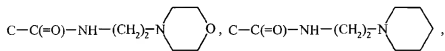
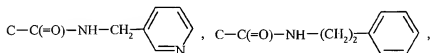
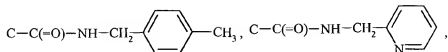
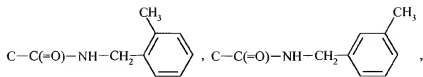
101. A compound according to claim 89 wherein W represents CH; X represents CH; Y represents

25 CH; Z represents CH or C-CH₃; R⁷ represents hydrogen; and  represents a cyclopentyl, cyclohexyl or cycloheptyl ring; and q is zero.

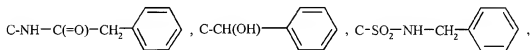
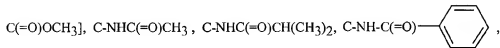
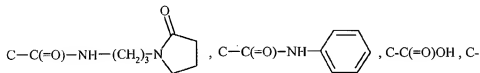
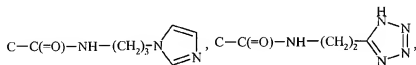
102. A compound according to claim 89 wherein W represents CH; X represents CH; Z represents CH; Y represents C-C₁₋₄alkyl, C-aryl, C-CN, C-NO₂, C-halo, C-haloalkyl, C-heteroaryl, C-OR⁴, C-C(=O)R⁴, C-C(=O)NY¹Y², -C(=O)OR⁴, C-NHC(=O)R⁴, C-CH(OH)aryl, C-S(O)₂NY¹Y²,
 5 C-S(O)_nR⁴, R⁷ represents hydrogen;  represents a cyclopentyl, cyclohexyl or cycloheptyl

ring; and q is zero.

103. A compound according to claim 89 wherein W represents CH; X represents CH; Z represents CH; Y represents C-CH₃, C-CH₂CH₃, C-CH₂CH₂CH₃, C-CH(CH₃)₂, C-,
, , , ,
, , , , C-CN, C-
 NO₂, C-Br, C-Cl, C-F, C-CF₃, C-, C-, C-OCH₃,
 C-OCH₂CH₃, C-OCHF₂, C-OCF₃, C-O-, C-O-CH₂-,
 C-O-(CH₂)₂-, C-C(=O)R⁴, C-C(=O)-, C-C(=O)-NH-CH₃,
 15 C-C(=O)-N(CH₃)₂, C-C(=O)-NH-CH₂CH₃, C-C(=O)-NH-CH(CH₃)₂,
 C-C(=O)-NH-C(CH₃)₂-CH₂OH, C-C(=O)-NH-CH₂CH₂CN,
 C-C(=O)-NH-CH₂CH₂OCH₃, C-C(=O)-NH-CH₂-,



5




104. $\text{C}-\text{SO}_2\text{CH}_3$; R^7 represents hydrogen; A represents a cyclopentyl, cyclohexyl or


10 cycloheptyl ring; and q is zero.


105. A compound according to claim 89 wherein W represents CH ; X represents $\text{C}-\text{CH}_3$,

$\text{C}-\text{CH}_2\text{CH}_3$, $\text{C}-\text{CH}(\text{CH}_3)_2$, $\text{C}-\text{OCH}_3$, $\text{C}-\text{OCH}_2\text{CH}_3$, $\text{C}-\text{Br}$ or $\text{C}-\text{Cl}$; Y represents $\text{C}-\text{CH}_3$, $\text{C}-\text{CH}_2\text{CH}_3$,

15 $\text{C}-\text{OCH}_3$, $\text{C}-\text{Br}$, $\text{C}-\text{Cl}$, $\text{C}-\text{F}$, $\text{C}-\text{C}_6\text{H}_5$ or $\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}_2-\text{C}_6\text{H}_5$; Z represents CH ;

R^7 represents hydrogen;  represents a cyclopentyl, cyclohexyl or cycloheptyl ring; and q is zero.

106. A compound according to claim 89 wherein W represents CH; X represents CR^2 and Y represents CR^3 where R^2 and R^3 form the group $-CH_2-O-CH_2-$; Z represents CH; R^7 represents hydrogen;  represents a cyclopentyl, cyclohexyl or cycloheptyl ring; and q is zero.

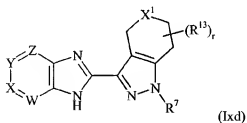
107. A compound according to claim 89 wherein W represents CH; X represents CR^2 and Y represents CR^3 where R^2 and R^3 form the group $-CH_2-CH_2-CH_2-$; Z represents CH; R^7 represents hydrogen;  represents a cyclopentyl, cyclohexyl or cycloheptyl ring; and q is zero.

108. A compound according to claim 89 wherein R^7 represents hydrogen and q is zero.

109. A compound according to claim 89 wherein W is CH; X is $C-CH_3$; Y is $C-CH_3$; and Z is CII.

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110. A compound according to claim 3 of the formula (Ixd)



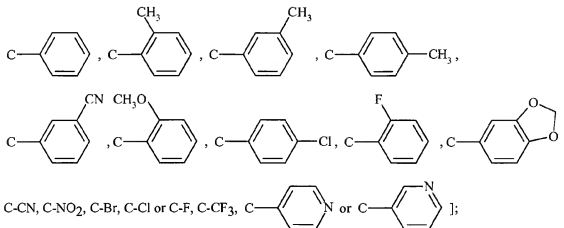
wherein


20 X^1 is O, S, SO_2 , or NY^5 , where Y^5 is hydrogen, R^4 , $-C(=O)R^4$, $-C(=O)NY^1Y^2$, $-C(=O)OR^4$ or Y^5 is $-SO_2R^4$; r is zero or an integer one or two; R^7 is hydrogen or alkyl; and R^{13} is alkyl or, when two R^{13} groups are attached to the same carbon atom, they form an oxo group; or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.

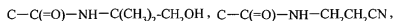
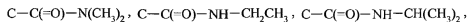
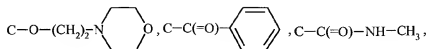
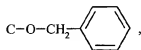
111. A compound according to claim 110 wherein W represents CH; X represents CH; Y represents CH; and Z represents CH or C-CH₃.

- 5 112. A compound according to claim 110 wherein W represents CH; X represents CH; Z represents CH; and Y represents C-C₁₋₄alkyl, C-aryl, C-CN, C-NO₂, C-halo, C-haloalkyl, C-heteroaryl, C-OR⁴, C-C(=O)R⁴, C-C(=O)NY¹Y², C-C(=O)OR⁴, C-NHC(=O)R⁴, C-CH(OH)aryl, C-S(O)₂NY¹Y² or C-S(O)_nR⁴.

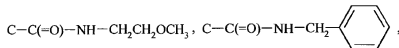
- 10 113. A compound according to claim 110 wherein W represents CH; X represents CH; Z represents CH; and Y represents C-CH₃, C-CH₂CH₃, C-CH₂CH₂CH₃ or C-CH(CH₃)₂,

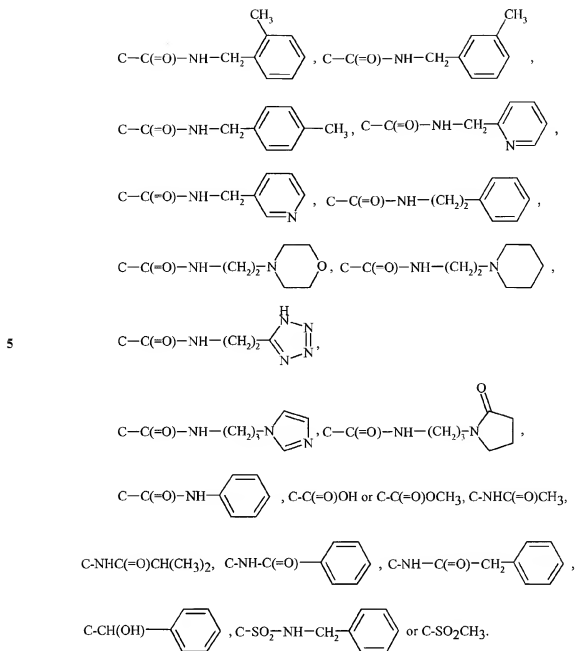


- 15 (viii) C-OR⁴ [e.g. C-OCH₃, C-OCH₂CH₃, C-OCHF₂, C-OCF₃, C-O-,



20









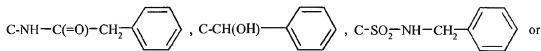
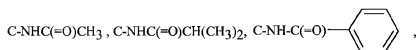
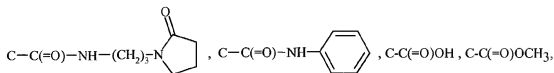
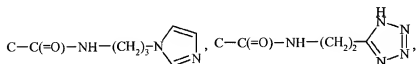
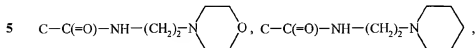
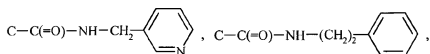
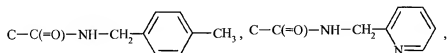
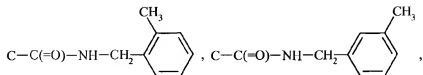
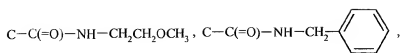
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114. A compound according to claim 110 wherein W represents CH; X represents C-CH₃, C-CH₂CH₃, C-CH(CH₃)₂, C-OCH₃, C-OCH₂CH₃, C-Br or C-Cl; Y represents C-CH₃, C-CH₂CH₃, C-OCH₃, C-Br, C-Cl, C-F, C-C₆H₄ or C-C(=O)-NH-CH₂-C₆H₄; and Z represents



CH.







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115. A compound according to claim 110 wherein W represents CH; X represents CH; Y represents C-CH₃; and Z represents C-CH₃.
116. A compound according to claim 110 wherein W represents CH; X represents CR² and Y represents CR³ where R² and R³ form the group -CH₂-O-CH₂-; and Z represents CH.
117. A compound according to claim 110 wherein W represents CH; X represents CR² and Y represents CR³ where R² and R³ form the group -CH₂-CH₂-CH₂-; and Z represents CH.
118. A compound according to claim 110 wherein R⁷ represents hydrogen.
119. A compound according to claim 110 wherein X¹ is O, N-C(=O)R⁴, N-C(=O)NY¹Y², N-C(=O)OR⁴, or N-SO₂R⁴; and r is zero.
120. A compound according to claim 110 wherein X¹ is O, N-C(=O)CH₃, N-C(=O)CH₂CH(CH₃)₂, N-C(=O)CH(CH₃)₂, N-C(=O)C(CH₃)₃, N-C(=O)-, N-C(=O)N(CH₃)₂, N-C(=O)NCH(CH₃)₂, N-C(=O)N(CH₂CH₃)₂, N-C(=O)-, N-C(=O)-, N-C(=O)-, N-C(=O)OCH₃, N-C(=O)OCH₂CH₃, N-SO₂CH₃ or N-SO₂CH(CH₃)₂; and r is zero.
121. A compound according to claim 110 wherein r is zero.
122. A compound according to claim 110 wherein W represents CH; X represents CH; Y represents CH; Z represents CH or C-CH₃; R⁷ represents hydrogen; X¹ is O, N-C(=O)R⁴, N-C(=O)NY¹Y², N-C(=O)OR⁴, N-SO₂R⁴; and r is zero.
123. A compound according to claim 110 wherein W represents CH; X represents CH; Y represents CH; Z represents CH or C-CH₃; R⁷ represents hydrogen; X¹ is O, N-C(=O)CH₃, N-




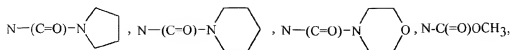
- 10 $\text{C}-\text{SO}_2\text{CH}_3$; R^7 represents hydrogen; X^1 is O, $\text{N}-\text{C}(=\text{O})\text{CH}_3$, $\text{N}-\text{C}(=\text{O})\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{CH}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{C}(\text{CH}_3)_3$, $\text{N}-(\text{C}=\text{O})-\text{C}_2\text{H}_4$, $\text{N}-\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{NCH}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$, $\text{N}-(\text{C}=\text{O})-\text{C}_4\text{H}_8$, $\text{N}-(\text{C}=\text{O})-\text{C}_6\text{H}_{10}$, $\text{N}-(\text{C}=\text{O})-\text{N}(\text{C}_2\text{H}_4)_2\text{O}$, $\text{N}-\text{C}(=\text{O})\text{OCH}_3$, $\text{N}-\text{C}(=\text{O})\text{OCH}_2\text{CH}_3$, $\text{N}-\text{SO}_2\text{CH}_3$ or $\text{N}-\text{SO}_2\text{CH}(\text{CH}_3)_2$; and r is zero.

126. A compound according to claim 110 wherein W represents CH; X represents C-CH₃, C-CH₂CH₃, C-CH(CH₃)₂, C-OCH₃, C-OCH₂CH₃, C-Br or C-Cl; Y represents C-CH₃, C-CH₂CH₃, C-OCH₃, C-Br, C-Cl, C-F, C- or C-C(=O)-NH-CH₂-; Z represents CH; R⁷ represents hydrogen; X¹ is O, N-C(=O)R⁴, N-C(=O)NY¹Y², N-C(=O)OR⁴ or N-SO₂R⁴; and r is zero.

127. W represents CH; X represents C-CH₃, C-CH₂CH₃, C-CH(CH₃)₂, C-OCH₃, C-OCH₂CH₃, C-Br or C-Cl; Y represents C-CH₃, C-CH₂CH₃, C-OCH₃, C-Br, C-Cl, C-F, C- or C-C(=O)-NH-CH₂-; Z represents CH; R⁷ represents hydrogen; X¹ is O,
- 10 N-C(=O)CH₃, N-C(=O)CH₂CH(CH₃)₂, N-C(=O)CH(CH₃)₂, N-C(=O)C(CH₃)₃ or N-(C=O)-, N-C(=O)N(CH₃)₂, N-C(=O)NCH(CH₃)₂, N-C(=O)N(CH₂CH₃)₂
- N-(C=O)-N-, N-(C=O)-N-, N-(C=O)-N-, N-C(=O)OCH₃, N-C(=O)OCH₂CH₃, N-SO₂CH₃ or N-SO₂CH(CH₃)₂; and r is zero.

- 15 128. A compound according to claim 110 wherein W represents CH; X represents CH; Y represents C-Cl₃; Z represents C-Cl₃; R⁷ represents hydrogen; X¹ is O, N-C(=O)R⁴, N-C(=O)NY¹Y², N-C(=O)OR⁴ or N-SO₂R⁴; and r is zero.

129. A compound according to claim 110 wherein W represents CH; X represents CH; Y represents C-CH₃; Z represents C-CH₃; R⁷ represents hydrogen; X¹ is O, N-C(=O)CH₃, N-C(=O)CH₂CH(CH₃)₂, N-C(=O)CH(CH₃)₂, N-C(=O)C(CH₃)₃ or N-(C=O)-, N-C(=O)N(CH₃)₂, N-C(=O)NCH(CH₃)₂, N-C(=O)N(CH₂CH₃)₂
- 20

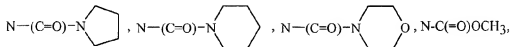
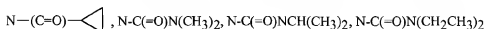


$\text{N}-\text{C}(=\text{O})\text{OCH}_2\text{CH}_3$, $\text{N}-\text{SO}_2\text{CH}_3$ or $\text{N}-\text{SO}_2\text{CH}(\text{CH}_3)_2$; and r is zero.

130. A compound according to claim 110 wherein W represents CH ; X represents CR^2 and Y represents CR^3 where R^2 and R^3 form the group $-\text{CH}_2-\text{O}-\text{CH}_2-$; Z represents CH ; R^7 represents hydrogen; X^1 is O , $\text{N}-\text{C}(=\text{O})\text{R}^4$, $\text{N}-\text{C}(=\text{O})\text{NY}^1\text{Y}^2$, $\text{N}-\text{C}(=\text{O})\text{OR}^4$ or $\text{N}-\text{SO}_2\text{R}^4$; and r is zero.

131. A compound according to claim wherein W represents CH ; X represents CR^2 and Y represents CR^3 where R^2 and R^3 form the group $-\text{CH}_2-\text{O}-\text{CH}_2-$; Z represents CH ; R^7 represents hydrogen; X^1 is O ,

$\text{N}-\text{C}(=\text{O})\text{CH}_3$, $\text{N}-\text{C}(=\text{O})\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{CH}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{C}(\text{CH}_3)_3$ or



$\text{N}-\text{C}(=\text{O})\text{OCH}_2\text{CH}_3$, $\text{N}-\text{SO}_2\text{CH}_3$ or $\text{N}-\text{SO}_2\text{CH}(\text{CH}_3)_2$; and r is zero.

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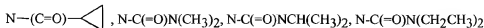
132. A compound according to claim 110 wherein




W represents CH ; X represents CR^2 and Y represents CR^3 where R^2 and R^3 form the group $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$; Z represents CH ; R^7 represents hydrogen; X^1 is O , $\text{N}-\text{C}(=\text{O})\text{R}^4$, $\text{N}-\text{C}(=\text{O})\text{NY}^1\text{Y}^2$, $\text{N}-\text{C}(=\text{O})\text{OR}^4$ or $\text{N}-\text{SO}_2\text{R}^4$; and r is zero.

20





133. A compound according to claim 110 wherein

W represents CH ; X represents CR^2 and Y represents CR^3 where R^2 and R^3 form the group $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$; Z represents CH ; R^7 represents hydrogen; X^1 is O , $\text{N}-\text{C}(=\text{O})\text{CH}_3$, $\text{N}-\text{C}(=\text{O})\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{CH}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{C}(\text{CH}_3)_3$ or













$\text{N}-(\text{C}=\text{O})-\text{N}$ , $\text{N}-(\text{C}=\text{O})-\text{N}$ , $\text{N}-(\text{C}=\text{O})-\text{N}$ , $\text{N}-\text{C}(=\text{O})\text{OCH}_3$,
 $\text{N}-\text{C}(=\text{O})\text{OCH}_2\text{CH}_3$, $\text{N}-\text{SO}_2\text{CH}_3$ or $\text{N}-\text{SO}_2\text{CH}(\text{CH}_3)_2$; and r is zero.

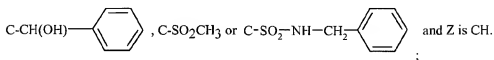
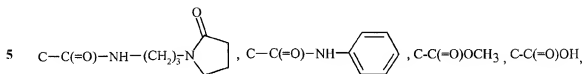
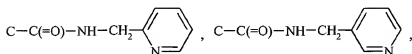
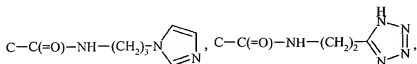
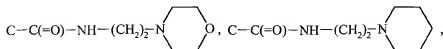
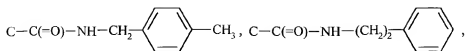
134. A compound according to claim 110 wherein

- 5 X^1 is $\text{N}-\text{C}(=\text{O})\text{CH}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{C}(\text{CH}_3)_3$; $\text{N}-(\text{C}=\text{O})$ ,
- $\text{N}-\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{NCH}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$, $\text{N}-(\text{C}=\text{O})-\text{N}$ ,
 $\text{N}-(\text{C}=\text{O})-\text{N}$ , $\text{N}-(\text{C}=\text{O})-\text{N}$ , $\text{N}-\text{C}(=\text{O})\text{OCH}_3$ or $\text{N}-\text{C}(=\text{O})\text{OCH}_2\text{CH}_3$; and r is zero.

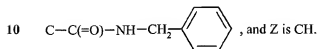
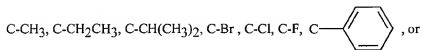
- 10 135. A compound according to claim 110 wherein W is CH_3 ; X is CH_3 ; Y is CH_3 , $\text{C}-\text{CH}_2\text{CH}_3$,

$\text{C}-\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{C}-$ , $\text{C}-$ , $\text{C}-$ , $\text{C}-$ ,
 $\text{C}-\text{CN}$, $\text{C}-\text{Br}$, $\text{C}-\text{CF}_3$, $\text{C}-$ , $\text{C}-$ , $\text{C}-\text{OCH}_3$, $\text{C}-\text{OCH}_2\text{CH}_3$, $\text{C}-\text{OCHF}_2$,
 $\text{C}-\text{OCF}_3$, $\text{C}-\text{O}-\text{CH}_2-$ , $\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}_3$, $\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_3$,
 $\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}(\text{CH}_3)_2$, $\text{C}-\text{C}(=\text{O})-\text{NH}-\text{C}(\text{CH}_3)_2-\text{CH}_2\text{OH}$, $\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_2\text{CN}$,

- 15 $\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}_2-$ ,
- $\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}_2-$ , $\text{C}-\text{C}(=\text{O})-\text{NH}-\text{CH}_2-$ ,



136. A compound according to claim 110 wherein W is CH; X is C-CH₃ or C-CH₂CH₃; Y is



137. A compound according to claim 110 wherein W is CH; X is C-OCH₃; Y is CH, C-CH₃, C-CH₂CH₃, C-Cl or C-OCH₃; and Z is CH.

15 138. A compound according to claim 110 wherein W is CH; X is C-OCH₂CH₃; Y is C-F; and Z is CH.

139. A compound according to claim 110 wherein W represents CH; X represents CR² and Y represents CR³ where R² and R³ form the group -CH₂-CH₂-CH₂-; and Z represents CH.

140. A compound according to claim 110 wherein W represents CH; X represents CR² and Y represents CR³ where R² and R³ form the group -CH₂-O-CH₂-; and Z represents CH.
- 5 141. A compound according to claim 110 wherein X¹ is $\text{N}-(\text{C}=\text{O})-\text{C}_1\text{H}_2$,
 $\text{N}-\text{C}(=\text{O})\text{N}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{NCH}(\text{CH}_3)_2$, $\text{N}-\text{C}(=\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$, $\text{N}-(\text{C}=\text{O})-\text{N}-\text{C}_4\text{H}_7$ or
 $\text{N}-(\text{C}=\text{O})-\text{N}-\text{C}_6\text{H}_{11}$ and r is zero;
 ;
142. A compound according to claim 110 wherein W represents CH; X represents C-CH₃; Y
 10 represents C-CH₃ or C-Cl; and Z represents CH.
143. A compound according to claim 3 which is
- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-methylamide;
 15 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-ethylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-isopropylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-phenylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-phenethylamide;
 5,6-dimethyl-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1H-benzimidazole;
 20 6-chloro-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1H-benzimidazole;
 6-chloro-2-(5-ethylsulfonyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole;
 2-(5-methylsulfonyl-1H-pyrazol-3-yl)-5-trifluoromethyl-1H-benzimidazole;
 2-(5-cyclopropylmethylsulfonyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
 2-(5-ethylsulfonyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
 25 5,6-dimethyl-2-[5-(pyridin-3-ylmethylsulfonyl)-1H-pyrazol-3-yl]-1H-benzimidazole;
 5-fluoro-2-[5-(methylsulfonyl)-1H-pyrazol-3-yl]-1H-benzimidazole;
 5,6-dimethyl-2-(5-phenethylsulfonyl-1H-pyrazol-3-yl)-1H-benzimidazole;
 4-methyl-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1H-benzimidazole;
 5,6-dimethyl-2-(5-benzylsulfonyl-1H-pyrazol-3-yl)-1H-benzimidazole;
 30 6-chloro-5-methyl-2-(5-morpholin-4-yl-1H-pyrazol-3-yl)-1H-benzimidazole;

- 5,6-dimethyl-2-[5-(thiophen-2-ylmethylsulfanyl)-1H-pyrazol-3-yl]-1H-benzimidazole;
2-(5-ethylsulfanyl-1H-pyrazol-3-yl)-5-methoxy-1H-benzimidazole hydrochloride;
5-methyl-2-(5-methylsulfanyl-4-propyl-1H-pyrazol-3-yl)-1H-benzimidazole;
2-(5-(4-methoxy-benzylsulfanyl)-4-propyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole;
- 5 2-(5-benzylsulfanyl-4-isopropyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole;
2-(5-methylsulfanyl-4-methyl-1H-pyrazol-3-yl)-5-methoxy-1H-benzimidazole;
2-(5-methylsulfanyl-4-methyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole;
3-(5-chloro-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
3-(5,6-dichloro-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
- 10 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
3-(5-ethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
- 15 3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
3-(5-trifluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
2-(4-amino-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid methyl ester;
3-(1H-benzimidazol-2-yl)-1H-indazole;
- 20 3-(5-methoxy-1H-benzimidazol-2-yl)-1H-indazole;
[2-(indazol-3-yl)-1H-benzimidazol-5-yl]-phenyl-methanone;
2-(1H-indazol-3-yl)-3H-benzimidazol-4-ol;
2-phenyl-1H-imidazol[4,5-b]pyrazine;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole;
- 25 2-(1H-indazol-3-yl)-3H-imidazo[4,5-c]pyridine;
2-(1H-indazole-3-yl)-3H-imidazo[4,5-b]pyridine;
2-(1H-pyrazol-3yl)-1H-benzimidazole;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methoxy-1H-indazole;
3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-5-methoxy-1H-indazole;
- 30 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-fluoro-1H-indazole;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-fluoro-1H-indazole;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-indazole;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-methoxy-1H-indazole;
5,6-dimethyl-2-(4-phenyl-1H-pyrazol-3-yl)-1H-benzimidazole;
- 35 3-(5-ethyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole;

- 3-(5-isopropyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-bromo-6-methyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-bromo-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-(3-cyano)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
5 3-(5-(pyrid-3-yl)-1H-benzimidazol-2-yl)-1H-indazole;
3-(6-methyl-5-phenyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-phenyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-(2-fluoro)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-(5,6-methylenedioxy)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
10 3-(5-(2-methoxy)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-(4-chloro)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-(4-methyl)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-benzyloxy-1H-benzimidazol-2-yl)-1H-indazole;
3-(5,6-methylenedioxy-1H-benzimidazol-2-yl)-1H-indazole;
15 3-(5,6-dimethoxy-1H-benzimidazol-2-yl)-1H-indazole;
3-(5,6-diethyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(4,5-dimethyl-1H-benzimidazol-2-yl)-1H-indazole;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carbonitrile;
3-(5-methoxycarbonyl-1H-benzimidazol-2-yl)-1H-indazole;
20 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-ethoxy-1H-indazole;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-pyrazole-4-carboxylic acid ethyl ester;
2-(4-isopropylcarbonyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid methyl ester;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-pyrazole-4-carboxylic acid ethyl ester;
3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide;
25 3-(5-methoxy-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1H-indazole;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid propylamide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide;
30 3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole-5-carbonitrile;
3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide;
3-(6-ethyl-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole-5-carbonitrile;
35 2-(5-methyl-1H-pyrazol-3-yl)-1H-benzimidazole;
2-(5-ethoxy-1H-pyrazol-3-yl)-1H-benzimidazole;

- 2-(5-methylsulfonyl-isoxazol-3-yl)-1H-benzimidazole;
 5-chloro-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole;
 5,6-dichloro-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole;
 (benzimidazol-2-yl)-5-methylthio-3-pyrazole;
- 5 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-indazole;
 2-(5-isopropyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
 2-(5-ethyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
 5,6-dimethyl-2-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-1H-benzimidazole;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4-fluoro-1H-indazole;
- 10 4-chloro-3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-chloro-1H-indazole;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazol-5-ol;
 3-(5-n-propyl-1H-benzimidazol-2-yl)-1H-indazole;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-sulfonic acid benzylamide;
- 15 3-(5-methanesulfonyl-1H-benzimidazol-2-yl)-1H-indazole;
 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-phenyl-methanol;
 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid;
 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, methylamide;
 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, dimethylamide;
- 20 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, isopropylamide;
 1H-benzimidazol-5-yl]-carboxylic acid, benzylamide;
 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, benzamide;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (2-hydroxy-1,1-dimethyl-
- 25 ethyl)-amide;
 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid cyclopropylamide;
 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid phenylmethyl-amide;
- 30 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-methyl-benzylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-methyl-benzylamide;
- 35 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;

- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-cyano-ethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide;
2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-imidazol-1-yl-propyl)-amide;
- 5 3-(5, 6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isobutylamide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylmethylamide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid tert-butylamide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole-5-carboxylic acid dimethylamide;
- 10 2-(4-isobutrylamino-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide;
[2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid;
3-(5,6-dimethyl-1H-benzimidazol-5-yl)-pyrazole-4-carboxylic acid;
2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-pyrazole-4-carboxylic acid;
- 15 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isobutyramide ;
N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-butyramide;
N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-phenyl-acetamide;
cyclopropanecarboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
methoxyacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 20 cyclopentanecarboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
trimethylacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
tert-butylacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
butanoic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
isoxazole-5-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 25 S(+)-2-methylbutanoic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
piperidine-1-carboxylic acid[3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
3-[3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethylurea;
cyclopropanecarboxylic acid [3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 30 cyclopropanecarboxylic acid [3-(5-ethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(5-trifluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
N-[3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isobutyramide;
- 35 cyclopropanecarboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;

- 3,5-dimethyl-isoxazole-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide;
- furan-3-carboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 5 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-4-methyl-benzamide;
- 5,6-dimethyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole;
- 5-ethyl-6-methyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole;
- 6-chloro-5-methoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole;
- 5-fluoro-6-methyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole;
- 10 2-(4-nitro-1H-pyrazol-3-yl)-5-trifluoromethoxy-1H-benzimidazole;
- 2-(4-nitro-1H-pyrazol-3-yl)-5-trifluoromethyl-1H-benzimidazole;
- 5-chloro-6-methyl-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole;
- 2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid methyl ester;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid
- 15 isopropylamide;
- cyclopropyl-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-methanone;
- isopropyl-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-methanone;
- 20 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-2,2-dimethyl-propan-1-one;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid methyl ester;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine;
- 25 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine;
- 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine;
- 3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid
- 30 *tert*-butyl ester;
- 5-methoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole;
- 5-ethoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole;
- 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester;
- 35 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester;

- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrano[4,3-c]pyrazole;
 3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester;
 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-morpholin-4-yl-acetamide;
- 5 2-dimethylamino-N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide;
 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(1H-1,2,3,4-tetraazol-1-yl)-acetamide;
 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isonicotinamide;
 2-cyclopropyl-N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide;
 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
- 10 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-isopropyl-urea;
 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-phenyl-urea;
 1-benzyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid isopropylamide;
- 15 cyclopropanecarboxylic acid[3-(5-ethoxy-6-ethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
 3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-ylamine;
 4-methylpiperazine-1-carboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]amide;
 1,1-dimethyl-3-[3-(1,5,6,7-tetrahydro-s-indacen-2-yl)-1H-pyrazol-4-yl]urea;
- 20 cyclopropanecarboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
 tetrahydropyran-4-carboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazole-4-yl]amide;
 morpholine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
 piperidine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
- 25 3-[6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethylurea;
 5-methoxy-2-(4-nitro-1H-pyrazol-3-yl)-1H-benzimidazole;
 morpholine-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylmethyl]-amide;
 3-[3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea;
- 30 piperidine-1-carboxylic acid [3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 cyclopropanecarboxylic acid [3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 cyclopropanecarboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]amide;
 morpholine-4-carboxylic acid[3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]-amide;
 piperidine-1-carboxylic acid [3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 35 3-[3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea;
 piperidine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;

- 3-[3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea;
morpholine-4-carboxylic acid [3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide;
- 5 [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-pyrrolidin-1-yl-methanone;
[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-piperidin-1-yl-methanone;
[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-morpholin-4-yl-methanone;
- 10 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide;
morpholine-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
piperidine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 15 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide;
3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [2-(2H-tetrazol-5-yl)-ethyl]-amide;
- 20 1-cyclopropyl-3-[3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
1-[3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
4-methyl-piperazine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
piperidine-1-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 25 1-[3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
morpholine-4-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
4-methyl-piperazine-1-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
1-methyl-3-[3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
- 30 1-[3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
4-methyl-piperazine-1-carboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
1-tert-butyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-ethyl-urea;
- 35 4-methyl-piperazine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;

- 1-cyclopropyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea;
 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-isobutyl-urea;
 1-cyclopropylmethyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
- 5 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
 3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole-5-carboxylic acid amide dihydrochloride;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole-5-carboxylic acid;
 2-(4-isobutyrylamino-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid;
 3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea;
- 10 3-(5-nitro-1H-benzimidazol-2-yl)-1H-indazole;
 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-piperidin-1-yl-ethyl)-amide;
 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide;
 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide;
 N-[2-(1H-Indazol-3-yl)-1H-benzimidazol-5-yl]-isobutyramide;
- 15 N-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-piperidin-1-yl-acetamide;
 2-(1H-indazol-3-yl)-3H-benzimidazol-5-amine; or
 piperidine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide; or
 or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such
 compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
- 20
144. A compound according to claim 14 which is
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-methylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-ethylamide;
- 25 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-isopropylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-phenylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-phenethylamide;
 5,6-dimethyl-2-(5-methylsulfanyl-1H-pyrazol-3-yl)-1H-benzimidazole;
 6-chloro-5-methyl-2-(5-methylsulfanyl-1H-pyrazol-3-yl)-1H-benzimidazole;
- 30 6-chloro-2-(5-ethylsulfanyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole;
 2-(5-methylsulfanyl-1H-pyrazol-3-yl)-5-trifluoromethyl-1H-benzimidazole;
 2-(5-cyclopropylmethylsulfanyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
 2-(5-ethylsulfanyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
 5,6-dimethyl-2-[5-(pyridin-3-ylmethylsulfanyl)-1H-pyrazol-3-yl]-1H-benzimidazole;
- 35 5-fluoro-2-[5-methylsulfanyl]-1H-pyrazol-3-yl]-1H-benzimidazole;
 5,6-dimethyl-2-(5-phenethylsulfanyl-1H-pyrazol-3-yl)-1H-benzimidazole;

- 4-methyl-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1H-benzimidazole;
5,6-dimethyl-2-(5-benzylsulfonyl-1H-pyrazol-3-yl)-1H-benzimidazole;
5,6-dimethyl-2-[5-(thiophen-2-ylmethylsulfonyl)-1H-pyrazol-3-yl]-1H-benzimidazole;
2-(5-ethylsulfonyl-1H-pyrazol-3-yl)-5-methoxy-1H-benzimidazole hydrochloride;
- 5 5-methyl-2-(5-methylsulfonyl-4-propyl-1H-pyrazol-3-yl)-1H-benzimidazole;
2-(5-(4-methoxy-benzylsulfonyl)-4-propyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole;
2-(5-benzylsulfonyl-4-isopropyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole;
2-(5-methylsulfonyl-4-methyl-1H-pyrazol-3-yl)-5-methoxy-1H-benzimidazole;
2-(5-methylsulfonyl-4-methyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole;
- 10 3-(5-chloro-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
3-(5,6-dichloro-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylamine;
5,6-dimethyl-2-(4-phenyl-1H-pyrazol-3-yl)-1H-benzimidazole;
3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide;
3-(5-methoxy-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
- 15 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid propylamide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide;
3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide;
- 20 3-(6-ethyl-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
2-(5-ethoxy-1H-pyrazol-3-yl)-1H-benzimidazole;
(benzimidazol-2-yl)-5-methylthio-3-pyrazole;
2-(5-isopropyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
2-(5-ethyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
- 25 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide;
2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide;
- 30 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid cyclopropylamide;
2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid phenylmethyl-amide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isobutyl-amide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylmethyl-amide;
- 35 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid tert-butylamide;
2-(4-isobutrylamino-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide;

- N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isobutyramide;
N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-butyramide;
N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-phenyl-acetamide;
cyclopropanecarboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
5 methoxyacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopentanecarboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
trimethylacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
tert-butylacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
butanoic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
10 isoxazole-5-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
S(+)-2-methylbutanoic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
piperidine-1-carboxylic acid [3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
3-[3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethylurea;
15 cyclopropanecarboxylic acid [3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(5-ethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(5-trifluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
20 N-[3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isobutyramide;
cyclopropanecarboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
3,5-dimethyl-isoxazole-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide;
25 furan-3-carboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-4-methyl-benzamide;
N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-morpholin-4-yl-acetamide;
2-dimethylamino-N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide;
N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(1H-1,2,3,4-tetraazol-1-yl)-acetamide;
30 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isonicotinamide;
2-cyclopropyl-N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide;
1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-isopropyl-urea;
1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-phenyl-urea;
35 1-benzyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
cyclopropanecarboxylic acid [3-(5-ethoxy-6-ethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;

- 4-methylpiperazine-1-carboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]amide;
1,1-dimethyl-3-[3-(1,5,6,7-tetrahydro-s-indacen-2-yl)-1H-pyrazol-4-yl]urea;
cyclopropanecarboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
- 5 tetrahydropyran-4-carboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazole-4-yl]amide;
morpholine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
piperidine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
3-[6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethylurea;
- 10 morpholine-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylmethyl]-amide;
3-[3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea;
piperidine-1-carboxylic acid [3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 15 cyclopropanecarboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]amide;
morpholine-4-carboxylic acid[3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]-amide;
piperidine-1-carboxylic acid [3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
3-[3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea;
piperidine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 20 3-[3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea;
morpholine-4-carboxylic acid [3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
morpholine-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
piperidine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
1-cyclopropyl-3-[3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
- 25 1-[3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
4-methyl-piperazine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
piperidine-1-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
1-[3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
- 30 morpholine-4-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
4-methyl-piperazine-1-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
1-methyl-3-[3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
1-[3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
- 35 4-methyl-piperazine-1-carboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;

- 1-tert-butyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-ethyl-urea;
 4-methyl-piperazine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 5 1-cyclopropyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea;
 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-isobutyl-urea;
 1-cyclopropylmethyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea;
- 10 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-piperidin-1-yl-ethyl)-amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide;
 N-[2-(1H-indazol-3-yl)-1H-benzimidazole-5-yl]-isobutyramide;
 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-piperidin-1-yl-acetamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-morpholinoamide;
- 15 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(N-methylpiperazino)amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-pyrrolidinoamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(isobutyl)amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(cyclohexylmethyl)amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(2-furfuryl)amide;
- 20 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-benzyl-N-methylamide;
 methyl 2-(1H-indazol-3-yl)-3H-benzimidazole-5-carboxylate;
 5,6-dimethyl-2-(1H-indazol-3-yl)-1H-benzimidazole;
 2-(1H-indazol-3-yl)-3H-benzimidazole-4-carboxylic acid;
 2-(5-ethoxy-2H-pyrazol-3-yl)-1H-benzimidazole-4-carboxylic acid;
- 25 5,6-dimethyl-2-(5-methyl-2H-pyrazol-3-yl)-1H-benzimidazole;
 5,6-dimethyl-2-(5-thiophen-2-yl-2H-pyrazol-3-yl)-1H-benzimidazole;
 2-(4-bromo-2H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
 2-(5-ethyl-2H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
 2-(5-ethyl-2H-pyrazol-3-yl)-4,5-ethylenedioxy-1H-benzimidazole;
- 30 2-(5-ethyl-2H-pyrazol-3-yl)-5-methoxy-1H-benzimidazole;
 2-(5-ethyl-2H-pyrazol-3-yl)-4-hydroxy-1H-benzimidazole
 2-(5-ethyl-2H-pyrazol-3-yl)-5-bromo-1H-benzimidazole; or
 or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
- 35 145. A compound according to claim 14 which is

- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-methylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-ethylamide, Example 3;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-isopropylamide;
- 5 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-phenylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-phenethylamide;
5,6-dimethyl-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-1H-benzimidazole;
6-chloro-2-(5-methylsulfonyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole;
6-chloro-2-(5-ethylsulfonyl-1H-pyrazol-3-yl)-5-methyl-1H-benzimidazole;
- 10 2-(5-methylsulfonyl-1H-pyrazol-3-yl)-5-trifluoromethyl-1H-benzimidazole;
2-(5-cyclopropylmethylsulfonyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
2-(5-ethylsulfonyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide;
3-(5-methoxy-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
- 15 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid propylamide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide;
3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide;
- 20 3-(6-ethyl-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
2-(5-isopropyl-1H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide;
- 25 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid cyclopropylamide;
2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid phenylmethyl-amide, (compound denoted as A17-B106);
- 30 3-(5, 6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isobutyl-amide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylmethyl-amide;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid tert-butylamide;
2-(4-isobutrylamino-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide;
- 35 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isobutyramide;
N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-butyramide;

- N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-phenyl-acetamide;
 cyclopropanecarboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 methoxyacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 cyclopentanecarboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 5 trimethylacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
tert-butylacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 butanoic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 isoxazole-5-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 S(+)-2-methylbutanoic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 10 cyclopropanecarboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 piperidine-1-carboxylic acid[3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 3-[3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethylurea;
 cyclopropanecarboxylic acid [3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 cyclopropanecarboxylic acid [3-(5-ethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 15 cyclopropanecarboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 cyclopropanecarboxylic acid [3-(5-trifluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 cyclopropanecarboxylic acid [3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 N-[3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isobutyramide;
 cyclopropanecarboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 20 3,5-dimethyl-isoxazole-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-
 amide;
 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide;
 furan-3-carboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-4-methyl-benzamide;
 25 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-morpholin-4-yl-acetamide;
 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]- 2-(1H-1,2,3,4-tetraazol-1-yl)-acetamide;
 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isonicotinamide;
 2-cyclopropyl-N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide;
 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
 30 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-isopropyl-urea;
 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-phenyl-urea;
 1-benzyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 cyclopropanecarboxylic acid[3-(5-ethoxy-6-ethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
 4-methylpiperazine-1-carboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-
 35 yl]amide;
 1,1-dimethyl-3-[3-(1,5,6,7-tetrahydro-s-indacen-2-yl)-1H-pyrazol-4-yl]urea;

- cyclopropanecarboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
tetrahydropyran-4-carboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazole-4-yl]amide;
morpholine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
- 5 piperidine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
3-[6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethylurea;
morpholine-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-ylmethyl]-amide;
- 3-[3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea, Example 257(h);
- 10 piperidine-1-carboxylic acid [3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]amide;
morpholine-4-carboxylic acid[3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]-amide;
piperidine-1-carboxylic acid [3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 15 3-[3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea;
piperidine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
3-[3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea;
morpholine-4-carboxylic acid [3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
morpholine-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 20 piperidine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
1-cyclopropyl-3-[3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
1-[3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
4-methyl-piperazine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 25 piperidine-1-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
1-[3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
morpholine-4-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
4-methyl-piperazine-1-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 30 1-methyl-3-[3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
1-[3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
4-methyl-piperazine-1-carboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
1-tert-butyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
- 35 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-ethyl-urea;

- 4-methyl-piperazine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 1-cyclopropyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
- 3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea;
- 5 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-isobutyl-urea;
- 1-cyclopropylmethyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
- 3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea;
- 2-[1H-Indazol-3-yl]-1H-benzimidazole-5-carboxylic acid (2-piperidin-1-yl-ethyl)-amide;
- 2-[1H-Indazol-3-yl]-1H-benzimidazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide; or
- 10 N-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-piperidin-1-yl-acetamide, or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
146. A compound according to claim 14 which is
- 15 3-(1,5,6,7-tetrahydro-1,3-diazas-indacen-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide;
- 3-(5-methoxy-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid propylamide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide;
- 20 3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
- 3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide;
- 3-(6-ethyl-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide;
- 25 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid cyclopropylamide;
- 2-(4-isopropylcarbamoyl-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid phenylmethyl-amide;
- 30 3-(5, 6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isobutyl-amide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylmethyl-amide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-pyrazole-4-carboxylic acid tert-butylamide;
- 2-(4-isobutylamino-1H-pyrazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide;
- 35 N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isobutylamide;
- N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-butylamide;

- cyclopropanecarboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
methoxyacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopentanecarboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
trimethylacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 5 *tert*-butylacetic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
butanoic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
isoxazole-5-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
S(+)-2-methylbutanoic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 10 piperidine-1-carboxylic acid[3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
3-[3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethylurea;
cyclopropanecarboxylic acid [3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(5-ethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
cyclopropanecarboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 15 cyclopropanecarboxylic acid [3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
N-[3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isobutyramide;
cyclopropanecarboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
3,5-dimethyl-isoxazole-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 20 furan-3-carboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-morpholin-4-yl-acetamide;
N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-(1H-1,2,3,4-tetraazol-1-yl)-acetamide;
N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-isonicotinamide;
2-cyclopropyl-N-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide;
- 25 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-isopropyl-urea;
1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-phenyl-urea;
1-benzyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
cyclopropanecarboxylic acid[3-(5-ethoxy-6-ethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
- 30 4-methylpiperazine-1-carboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]amide;
1,1-dimethyl-3-[3-(1,5,6,7-tetrahydro-s-indacen-2-yl)-1H-pyrazol-4-yl]urea;
cyclopropanecarboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
tetrahydropyran-4-carboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazole-4-yl]
- 35 y]amide;
morpholine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;

- piperidine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
 3-[6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethylurea;
 3-[3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea;
 piperidine-1-carboxylic acid [3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 5 cyclopropanecarboxylic acid [3-(6-chloro-5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 cyclopropanecarboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]amide;
 morpholine-4-carboxylic acid[3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]-amide;
 piperidine-1-carboxylic acid [3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 3-[3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea;
- 10 piperidine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 3-[3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea;
 morpholine-4-carboxylic acid [3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 morpholine-4-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 piperidine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 15 1-cyclopropyl-3-[3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 1-[3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
 4-methyl-piperazine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 piperidine-1-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 20 1-[3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
 morpholine-4-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 1-methyl-3-[3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 1-[3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-methyl-urea;
 4-methyl-piperazine-1-carboxylic acid [3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 25 1-tert-butyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-ethyl-urea;
 4-methyl-piperazine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
- 30 1-cyclopropyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea;
 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-3-isobutyl-urea;
 1-cyclopropylmethyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea; or
 3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea; or
- 35 an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound;
 or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.

147. A compound according to claim 14 which is
- 3-(5-methoxy-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isopropylamide;
 - 3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazole-4-carboxylic acid cyclopropylamide;
 - 5 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (tetrahydro-pyran-4-yl)-amide;
 - 3-(5, 6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid isobutyl-amide;
 - cyclopropanecarboxylic acid[3-(5-ethoxy-6-ethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
 - 1,1-dimethyl-3-[3-(1,5,6,7-tetrahydro-s-indacen-2-yl)-1H-pyrazol-4-yl]urea;
 - piperidine-4-carboxylic acid[3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide;
 - 10 3-[6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethylurea;
 - 3-[3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea;
 - piperidine-1-carboxylic acid [3-(5-difluoromethoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 - cyclopropanecarboxylic acid [3-(1,5,6,7-tetrahydro-1,3-diaza-s-indacen-2-yl)-1H-pyrazol-4-yl]amide;
 - piperidine-1-carboxylic acid [3-(5-methoxy-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 - 15 piperidine-1-carboxylic acid [3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 - piperidine-1-carboxylic acid [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 - 1-cyclopropyl-3-[3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 - piperidine-1-carboxylic acid [3-(5-fluoro-6-methyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-amide;
 - 1-tert-butyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 - 20 1-cyclopropyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea;
 - 3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-diethyl-urea;
 - 1-cyclopropylmethyl-3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-urea; or
 - 3-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-1,1-dimethyl-urea;
 - or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such
 - 25 compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
148. A compound according to claim 54 which is
- 3-(1H-benzimidazol-2-yl)-1H-indazole;
 - 3-(5-methoxy-1H-benzimidazol-2-yl)-1H-indazole;
 - 30 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-phenyl-methanone;
 - 2-(1H-indazol-3-yl)-3H-benzimidazol-4-ol;
 - 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole;
 - 2-(1H-indazol-3-yl)-3H-imidazo[4,5-c]pyridine;
 - 2-(1H-indazole-3-yl)-3H-imidazo[4,5-b]pyridine;
 - 35 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methoxy-1H-indazole;
 - 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-fluoro-1H-indazole;

- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-fluoro-1H-indazole;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-indazole;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-methoxy-1H-indazole;
3-(5-ethyl-1H-benzimidazol-2-yl)-1H-indazole;
5 3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-isopropyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-bromo-6-methyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-bromo-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-(3-cyano)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
10 3-(5-(pyrid-3-yl)-1H-benzimidazol-2-yl)-1H-indazole;
3-(6-methyl-5-phenyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-phenyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-(2-fluoro)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-(5,6-methylenedioxy)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
15 3-(5-(2-methoxy)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-(4-chloro)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-(4-methyl)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5-benzyloxy-1H-benzimidazol-2-yl)-1H-indazole;
3-(5,6-methylenedioxy-1H-benzimidazol-2-yl)-1H-indazole;
20 3-(5,6-dimethoxy-1H-benzimidazol-2-yl)-1H-indazole;
3-(5,6-diethyl-1H-benzimidazol-2-yl)-1H-indazole;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carbonitrile;
3-(5-methoxycarbonyl-1H-benzimidazol-2-yl)-1H-indazole;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-ethoxy-1H-indazole;
25 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1H-indazole;
3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole-5-carbonitrile;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole-5-carbonitrile;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4-fluoro-1H-indazole;
3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-chloro-1H-indazole;
30 3-(5-n-propyl-1H-benzimidazol-2-yl)-1H-indazole;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-sulfonic acid benzylamide;
3-(5-methanesulfonyl-1H-benzimidazol-2-yl)-1H-indazole;
[2-(indazol-3-yl)-1H-benzimidazol-5-yl]-phenyl-methanol;
[2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid;
35 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, methylamide;
[2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, dimethylamide;

- [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, isopropylamide;
 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, benzylamide;
 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, benzamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide;
 5 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-methyl-benzylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-methyl-benzylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide;
 10 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-cyano-ethyl)-amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide;
 2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-imidazol-1-yl-propyl)-amide;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole-5-carboxylic acid dimethylamide;
 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid; or
 15 or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
149. A compound according to claim 54 which is
- 3-(1H-benzimidazol-2-yl)-1H-indazole;
 20 3-(5-methoxy-1H-benzimidazol-2-yl)-1H-indazole;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methoxy-1H-indazole;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-fluoro-1H-indazole;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-fluoro-1H-indazole;
 25 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methyl-1H-indazole;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-6-methoxy-1H-indazole;
 3-(5-ethyl-1H-benzimidazol-2-yl)-1H-indazole;
 3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole;
 3-(5-isopropyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole;
 30 3-(5-bromo-6-methyl-1H-benzimidazol-2-yl)-1H-indazole;
 3-(5-bromo-1H-benzimidazol-2-yl)-1H-indazole;
 3-(5-(3-cyano)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
 3-(5-(pyrid-3-yl)-1H-benzimidazol-2-yl)-1H-indazole;
 3-(6-methyl-5-phenyl-1H-benzimidazol-2-yl)-1H-indazole;
 35 3-(5-phenyl-1H-benzimidazol-2-yl)-1H-indazole, (compound denoted as A60-B63), Example 235(q);
 3-(5-(2-fluoro)phenyl-1H-benzimidazol-2-yl)-1H-indazole;

- 3-(5-(3,4 -methylenedioxy)phenyl-1H-benzimidazol-2-yl)-1H-indazole;
- 3-(5-benzyloxy-1H-benzimidazol-2-yl)-1H-indazole;
- 3-(5,6-methylenedioxy-1H-benzimidazol-2-yl)-1H-indazole;
- 3-(5,6-dimethoxy-1H-benzimidazol-2-yl)-1H-indazole;
- 5 3-(5,6-diethyl-1H-benzimidazol-2-yl)-1H-indazole;
- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carbonitrile;
- 3-(5-methoxycarbonyl-1H-benzimidazol-2-yl)-1H-indazole;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-ethoxy-1H-indazole;
- 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1H-indazole;
- 10 3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole-5-carbonitrile;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole-5-carbonitrile;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4-fluoro-1H-indazole;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-chloro-1H-indazole;
- 3-(5-n-propyl-1H-benzimidazol-2-yl)-1H-indazole;
- 15 2-(1H-indazol-3-yl)-1H-benzimidazole-5-sulfonic acid benzylamide;
- 3-(5-methanesulfonyl-1H-benzimidazol-2-yl)-1H-indazole;
- [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-phenyl-methanol;
- [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, ethylamide;
- [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, methylamide;
- 20 [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, isopropylamide;
- [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, benzylamide;
- [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid, benzamide;
- [2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide;
- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-methyl-benzylamide;
- 25 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-methyl-benzylamide;
- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [3-(2-oxo-pyrrolidin-1-yl)-propyl]-amide;
- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;
- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide;
- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-cyano-ethyl)-amide;
- 30 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide;
- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-imidazol-1-yl-propyl)-amide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole-5-carboxylic acid dimethylamide;
- [2-(indazol-3-yl)-1H-benzimidazol-5-yl]-carboxylic acid;
- 3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole-5-carboxylic acid amide dihydrochloride;
- 35 or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.

150. A compound according to claim 54 which is
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-methoxy-1H-indazole;
 3-(5-ethyl-6-methyl-1H-benzimidazol-2-yl)-1H-indazole; or
 5 3-(5,6-diethyl-1H-benzimidazol-2-yl)-1H-indazole;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1H-indazole-5-carboxylic acid dimethylamide;
 or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such
 compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
- 10 151. A compound according to claim 89 which is
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-indazole;
 5,6-dimethyl-2-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-1H-benzimidazole;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,5,6,7,8-hexahydro-cycloheptapyrazole; or
 or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such
 15 compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
152. A compound according to claim 89 which is
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-4,5,6,7-tetrahydro-1H-indazole; or
 5,6-dimethyl-2-(1,4,5,6-tetrahydro-cyclopentapyrazol-3-yl)-1H-benzimidazole; or
 20 an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound;
 or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
153. A compound according to claim 110 which is
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid
 25 isopropylamide;
 cyclopropyl-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-
 methanone;
 isopropyl-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-
 methanone;
 30 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethanone;
 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-methyl-
 propan-1-one;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid
 methyl ester;
 35 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid
 dimethylamide;

- 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-3-methylbutan-1-one;
- 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-2,2-dimethyl-propan-1-one;
- 5 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid methyl ester;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid isopropylamide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide;
- 10 [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-pyrrolidin-1-yl-methanone;
- [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-piperidin-1-yl-methanone;
- 15 [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-morpholin-4-yl-methanone;
- 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide;
- 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-
- 20 carboxylic acid diethylamide;
- 3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide;
- 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-2,2-dimethyl-propan-1-one;
- 25 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-5-(propane-2-sulfonyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine; or
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyran[4,3-c]pyrazole; or
- an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound;
- or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
- 30 154. A compound according to claim 110 which is
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid isopropylamide;
- cyclopropyl-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-
- 35 methanone;

- isopropyl-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-methanone;
- 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-2,2-dimethyl-propan-1-one;
- 5 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid methyl ester;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid isopropylamide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide;
- 10 [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-pyrrolidin-1-yl-methanone;
- [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-piperidin-1-yl-methanone;
- 15 [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-morpholin-4-yl-methanone;
- 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide;
- 3-[5-(2-morpholin-4-yl-ethoxy)-1H-benzimidazol-2-yl]-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-
- 20 carboxylic acid diethylamide;
- 3-(5-trifluoromethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid diethylamide;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid dimethylamide;
- 25 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-methyl-propan-1-one;
- 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid methyl ester;
- 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-3-methyl-
- 30 butan-1-one; or
- 1-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-2,2-dimethyl-propan-1-one; or
- or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such
- 35 compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.

155. A compound according to claim 110 which is
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid
 isopropylamide;
 cyclopropyl-[3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-
 5 methanone;
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid
 isopropylamide;
 prepared 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-
 carboxylic acid diethylamide;
- 10 [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-pyrrolidin-1-
 yl-methanone;
 [3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl]-piperidin-1-
 yl-methanone;
 3-(5-chloro-6-methyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic
 15 acid diethylamide; or
 3-(5,6-dimethyl-1H-benzimidazol-2-yl)-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid
 dimethylamide;
 or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such
 compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
- 20
156. A compound according to claim 3 which is
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-methylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-ethylamide;
 25 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-isopropylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-phenylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-phenethylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-morpholinoamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(N'-methylpiperazino)amide;
 30 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-pyrrolidinoamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(isobutyl)amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(cyclohexylmethyl)amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(2-furfuryl)amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-benzyl-N-methylamide;
 35 methyl 2-(1H-indazol-3-yl)-3H-benzimidazole-5- carboxylate;
 5,6-dimethyl-2-(1H-indazol-3-yl)-1H-benzimidazole;

- 5-methoxy-2-(1H-indazol-3-yl)-1H-benzimidazole;
2-(1H-indazol-3-yl)-3H-benzimidazole-4-carboxylic acid;
5-bromo-2-(1H-indazol-3-yl)-3H-benzimidazole;
2-(5-ethoxy-2H-pyrazol-3-yl)-1H-benzimidazole-4-carboxylic acid;
5,6-dimethyl-2-(5-methyl-2H-pyrazol-3-yl)-1H-benzimidazole;
5,6-dimethyl-2-(5-thiophen-2-yl-2H-pyrazol-3-yl)-1H-benzimidazole;
2-(4-bromo-2H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
2-(5-ethyl-2H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
2-(5-ethyl-2H-pyrazol-3-yl)-4,5-ethylenedioxy-1H-benzimidazole;
10 2-(5-ethyl-2H-pyrazol-3-yl)-5-methoxy-1H-benzimidazole;
2-(5-ethyl-2H-pyrazol-3-yl)-4-hydroxy-1H-benzimidazole
2-(5-ethyl-2H-pyrazol-3-yl)-5-bromo-1H-benzimidazole;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 2,4-dichloro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (3-ethoxy-propyl)-amide;
15 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-bromo-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-methanesulfonyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (naphthalen-1-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-trifluoromethyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (thiophen-2-ylmethyl)-amide;
20 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-dimethylamino-benzylamide;
4-([2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carbonyl]-amino)-methyl-piperidine-1-carboxylic acid tert-butyl ester;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-nitro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide;
25 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 3-bromo-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 3-methoxy-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (benzo[b]thiophen-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (1,3-dimethyl-1H-pyrazol-4-ylmethyl)-
30 amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 2-trifluoromethoxy-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 2-methyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (3-methyl-thiophen-2-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 2-trifluoromethyl-benzylamide;
35 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-phenoxy-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 3-trifluoromethoxy-benzylamide;

- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-isopropoxy-propyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (1-methyl-1H-pyrazol-4-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-isopropyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,5-dimethyl-furan-3-ylmethyl)-amide;
5 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (benzo[b]thiophen-2-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [3-(3-acetylamino-phenoxy)-propyl]-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (6-chloro-pyridin-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid ([2,2']bithiophenyl-5-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,3-dihydro-benzofuran-5-ylmethyl)-
10 amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-cyano-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (5-chloro-benzo[b]thiophen-3-ylmethyl)-
amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-trifluoromethyl-benzylamide;
15 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-methylsulfanyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (benzo[b]thiophen-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-
amide;
20 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (furan-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-nitro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (thiophen-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3,5-dimethyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (1-methyl-1H-benzimidazol-2-ylmethyl)-
25 amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-methyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-chloro-benzylamide;
2-(1H-indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 4-sulfamoyl-benzylamide;
2-(1H-indazol-3-yl)-3H-benzimidazole-4-carboxylic acid (3-ethoxy-propyl)-amide;
30 2-(1H-indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 4-bromo-benzylamide;
2-(1H-indazol-3-yl)-3H-benzimidazole-4-carboxylic acid (naphthalen-1-ylmethyl)-amide;
2-(1H-indazol-3-yl)-3H-benzimidazole-4-carboxylic acid (thiophen-2-ylmethyl)-amide;
2-(1H-indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 4-dimethylamino-benzylamide;
2-(1H-indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 4-nitro-benzylamide;
35 2-(1H-indazol-3-yl)-3H-benzimidazole-4-carboxylic acid (pyridin-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 3-bromo-benzylamide;

- 2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 3-methoxy-benzylamide;
2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid (benzo[b]thiophen-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 4-phenoxy-benzylamide;
2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 3-trifluoromethoxy-benzylamide;
5 2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid (6-chloro-pyridin-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid (2,3-dihydro-benzofuran-5-ylmethyl)-amide;
2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 3-trifluoromethyl-benzylamide;
2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 2-methylsulfanyl-benzylamide;
10 2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid (furan-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 2-nitro-benzylamide;
2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 3,5-dimethyl-benzylamide;
2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 3-chloro-benzylamide;
2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid phenylamide;
15 2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid benzylamide;
2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid phenethyl-amide;
3-(6-phenyl-1H-benzoimidazol-2-yl)-2H-indazole;
3-[6-(2,4-dichloro-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
3-(6-naphthalen-1-yl-1H-benzoimidazol-2-yl)-2H-indazole;
20 3-[6-(4-fluoro-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
3-[6-(4-chloro-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
3-[6-(4-methoxy-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
3-[6-(3-chloro-4-fluoro-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
3-[6-(3,5-dichloro-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
25 3-(6-thianthren-1-yl-1H-benzoimidazol-2-yl)-2H-indazole;
3-(6-biphenyl-4-yl-1H-benzoimidazol-2-yl)-2H-indazole;
3-(6-p-tolyl-1H-benzoimidazol-2-yl)-2H-indazole;
3-(6-m-tolyl-1H-benzoimidazol-2-yl)-2H-indazole;
3-(6-o-tolyl-1H-benzoimidazol-2-yl)-2H-indazole;
30 3-(6-thiophen-3-yl-1H-benzoimidazol-2-yl)-2H-indazole;
3-[6-(3-trifluoromethyl-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
3-[6-(4-trifluoromethyl-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
3-[6-(3-chloro-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
3-[6-(3-methoxy-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
35 3-[6-(3,5-dimethyl-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
3-[6-(3,4-dimethyl-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;

- 3-(6-benzo[1,3]dioxol-5-yl)-1H-benzimidazol-2-yl)-2H-indazole;
 3-[6-(4-tert-butyl-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 3-(6-hex-1-enyl-1H-benzimidazol-2-yl)-2H-indazole;
 3-[6-(3,4-dimethoxy-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 5 3-[2-(2H-indazol-3-yl)-3H-benzimidazol-5-yl]-phenol;
 4-[2-(2H-indazol-3-yl)-3H-benzimidazol-5-yl]-phenol;
 3-[6-(3,4-dichloro-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 3-[6-(4-trifluoromethoxy-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 1-{4-[2-(2H-indazol-3-yl)-3H-benzimidazol-5-yl]-phenyl}-ethanone;
 10 3-(6-benzo[b]thiophen-2-yl)-1H-benzimidazol-2-yl)-2H-indazole;
 3-[6-(3,4,5-trimethoxy-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 1-{5-[2-(2H-indazol-3-yl)-3H-benzimidazol-5-yl]-thiophen-2-yl}-ethanone;
 1-{3-[2-(2H-indazol-3-yl)-3H-benzimidazol-5-yl]-phenyl}-ethanone;
 3-[6-(4-benzyloxy-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 15 3-[6-(2-fluoro-biphenyl-4-yl)-1H-benzimidazol-2-yl]-2H-indazole;
 3-(6-benzo[b]thiophen-3-yl)-1H-benzimidazol-2-yl)-2H-indazole;
 {3-[2-(2H-indazol-3-yl)-3H-benzimidazol-5-yl]-phenyl}-methanol;
 3-[6-(4-ethylsulfonyl-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 3-[6-(2,4-difluoro-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 20 3-[6-(3-trifluoromethoxy-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 3-[6-(4-fluoro-2-methyl-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 3-[6-[2-(4-fluoro-phenyl)-vinyl]-1H-benzimidazol-2-yl]-2H-indazole;
 3-{6-[2-(4-chloro-phenyl)-vinyl]-1H-benzimidazol-2-yl}-2H-indazole;
 3-{4-[2-(2H-indazol-3-yl)-3H-benzimidazol-5-yl]-phenyl}-propionic acid;
 25 {4-[2-(2H-indazol-3-yl)-3H-benzimidazol-5-yl]-phenyl}-methanol;
 3-(6-furan-2-yl)-1H-benzimidazol-2-yl)-2H-indazole;
 3-[6-(3-benzyloxy-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 3-[6-(4-isopropyl-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 3-[6-(4-methanesulfonyl-phenyl)-1H-benzimidazol-2-yl]-2H-indazole;
 30 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-acetylamino-benzylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid methylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid isopropylamide;
 [2-(1H-indazol-3-yl)-1H-benzimidazol-5-yl]-morpholin-4-yl-methanone;
 35 [2-(1H-indazol-3-yl)-1H-benzimidazol-5-yl]-(4-methyl-piperazin-1-yl)-methanone;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzyl-methyl-amide;

- 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 3-nitro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 2-fluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 2,4-difluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 2,6-difluoro-benzylamide;
- 5 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-bromo-2-fluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-chloro-2-fluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-bromo-2-fluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 3,4-difluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 3,4,5-trifluoro-benzylamide;
- 10 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (4'-chloro-biphenyl-4-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (3',5'-dichloro-biphenyl-4-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (4'-fluoro-biphenyl-4-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 2-fluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 2,6-difluoro-3-methyl-benzylamide;
- 15 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 2,4-dichloro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-chloro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-chloro-2-methyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 4-fluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2'-chloro-biphenyl-4-ylmethyl)-amide;
- 20 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (6-trifluoromethyl-pyridin-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (5-pyridin-2-yl-thiophen-2-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (3-imidazol-1-yl-propyl)-amide;
- 25 4-[2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2,6-difluoro-4-chloro-benzyl)amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2,4-dichloro-6-fluoro-benzyl)amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (3-fluoro-4-chloro-benzyl)amide;
2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (2-fluoro-4-chloro-6-methyl-benzyl)amide;
- 30 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;
2-[5-(benzyloxy)-2H-pyrazol-3-yl]-1H-benzoimidazole;
2-[5-(3-phenyl-allyloxy)-2H-pyrazol-3-yl]-1H-benzoimidazole;
2-[5-(2-methyl-allyloxy)-2H-pyrazol-3-yl]-1H-benzoimidazole;
2-[5-(3,7-dimethyl-octa-2,6-dienyloxy)-2H-pyrazol-3-yl]-1H-benzoimidazole;
- 35 2-[5-(3-bromo-benzyloxy)-2H-pyrazol-3-yl]-1H-benzoimidazole;
3-[5-(1H-benzoimidazol-2-yl)-1H-pyrazol-3-yloxy-methyl]-benzonitrile;

- 2-[5-(4-trifluoromethyl-benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
2-[5-(3,4-dichloro-benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
2-[5-pentafluorophenylmethoxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
2-[5-(4-*tert*-butyl-benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
5 2-[5-(2-benzenesulfonylmethyl-benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
4-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxymethyl]-benzonitrile;
2-[5-(biphenyl-4-ylmethoxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
2,3-dichloro-benzenesulfonic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
2-[5-(2-morpholin-4-yl-ethoxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
10 2-[5-(2-piperidin-1-yl-ethoxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
2-[5-(3-methoxy-benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-1-*p*-tolyl-ethanone;
1-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-3,3,4,4,4-pentafluoro-butan-2-one;
2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-1-biphenyl-4-yl-ethanone;
15 1-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-butan-2-one;
2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-1-(4-dimethylamino-phenyl)-ethanone;
2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-1-(3-phenyl-isoxazol-5-yl)-ethanone;
2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-*N*-phenyl-acetamide;
1-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-3,3-dimethyl-butan-2-one;
20 1-adamantan-1-yl-2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-ethanone;
2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-1-naphthalen-2-yl-ethanone;
4-[2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-acetyl]-benzonitrile;
6-[2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-acetyl]-3,4-dihydro-1H-quinolin-2-one;
2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-1-(4-trifluoromethoxy-phenyl)-ethanone;
25 5-[2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-acetyl]-2-chloro-benzenesulfonamide;
2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-1-(4-methoxy-phenyl)-ethanone;
2-[5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yloxy]-1-cyclopropyl-ethanone;
isonicotinic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
2,2-dimethyl-propionic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
30 benzyloxy-acetic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
benzoic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
4-methoxy-benzoic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
phenyl-acetic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
2,3,4,5,6-Pentafluoro-benzoic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
35 cyclopropanecarboxylic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
2,2,3,3,4,4,4-heptafluoro-butyric acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;

- cyclopentanecarboxylic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
 3-phenyl-propionic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
 biphenyl-4-carboxylic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
 3,5-bis-trifluoromethyl-benzoic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
- 5 4-trifluoromethyl-benzoic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
 thiophene-2-carboxylic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
 or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
- 10 157. A compound according to claim 14 which is
 2-(5-ethyl-2H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole; or
 2-(5-methyl-2H-pyrazol-3-yl)-5,6-dimethyl-1H-benzimidazole;
 or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
- 15 158. A compound according to claim 54 which is
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-methylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-ethylamide;
- 20 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-isopropylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-phenylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-phenethylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-morpholinoamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(N-methylpiperazino)amide;
- 25 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-pyrrolidinoamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(isobutyl)amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(cyclohexylmethyl)amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(2-furfuryl)amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-benzyl-N-methylamide;
- 30 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2,4-dichloro-benzylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-ethoxy-propyl)-amide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-bromo-benzylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-methanesulfonyl-benzylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (naphthalen-1-ylmethyl)-amide;
- 35 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-trifluoromethyl-benzylamide;
 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (thiophen-2-ylmethyl)-amide;

- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-dimethylamino-benzylamide;
4-([2-(1H-indazol-3-yl)-1H-benzimidazole-5-carbonyl]-amino)-methyl-piperidine-1-carboxylic acid tert-butyl ester;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-nitro-benzylamide;
- 5 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-bromo-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-methoxy-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (benzo[b]thiophen-3-ylmethyl)-amide;
- 10 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (1,3-dimethyl-1H-pyrazol-4-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-trifluoromethoxy-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-methyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-methyl-thiophen-2-ylmethyl)-amide;
- 15 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-trifluoromethyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-phenoxy-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-trifluoromethoxy-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-isopropoxy-propyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (1-methyl-1H-pyrazol-4-ylmethyl)-amide;
- 20 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-isopropyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,5-dimethyl-furan-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (benzo[b]thiophen-2-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [3-(3-acetyl-amino-phenoxy)-propyl]-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (6-chloro-pyridin-3-ylmethyl)-amide;
- 25 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid ([2,2']bithiophenyl-5-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,3-dihydro-benzofuran-5-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-cyano-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-methylsulfanyl-benzylamide;
- 30 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (benzo[b]thiophen-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (furan-3-ylmethyl)-amide;
- 35 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-nitro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (thiophen-3-ylmethyl)-amide;

- 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 3,5-dimethyl-benzylamide;
 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (1-methyl-1H-benzoimidazol-2-ylmethyl)-amide;
 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 3-methyl-benzylamide;
 5 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid 3-chloro-benzylamide;
 2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 4-sulfamoyl-benzylamide;
 2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid (pyridin-3-ylmethyl)-amide;
 2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 3-methoxy-benzylamide;
 2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 2-methylsulfanyl-benzylamide;
 10 2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid (furan-3-ylmethyl)-amide;
 2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 2-nitro-benzylamide;
 2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid 3,5-dimethyl-benzylamide;
 2-(1H-indazol-3-yl)-3H-benzoimidazole-4-carboxylic acid phenylamide;
 3-[6-(4-fluoro-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
 15 3-[6-(4-methoxy-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
 3-[6-(3-chloro-4-fluoro-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
 3-(6-m-tolyl-1H-benzoimidazol-2-yl)-2H-indazole;
 3-(6-o-tolyl-1H-benzoimidazol-2-yl)-2H-indazole;
 3-(6-thiophen-3-yl-1H-benzoimidazol-2-yl)-2H-indazole;
 20 3-[6-(3-chloro-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
 3-[6-(3-methoxy-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
 3-[6-(3,5-dimethyl-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
 3-(6-benzo[1,3]dioxol-5-yl-1H-benzoimidazol-2-yl)-2H-indazole;
 3-(6-hex-1-enyl-1H-benzoimidazol-2-yl)-2H-indazole;
 25 3-[6-(3,4-dimethoxy-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
 3-[2-(2H-indazol-3-yl)-3H-benzoimidazol-5-yl]-phenol;
 4-[2-(2H-indazol-3-yl)-3H-benzoimidazol-5-yl]-phenol;
 3-[6-(3,4,5-trimethoxy-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
 1-[5-[2-(2H-indazol-3-yl)-3H-benzoimidazol-5-yl]-thiophen-2-yl]-ethanone;
 30 {3-[2-(2H-indazol-3-yl)-3H-benzoimidazol-5-yl]-phenyl}-methanol;
 3-[6-(2,4-difluoro-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
 3-[6-(4-fluoro-2-methyl-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
 {4-[2-(2H-indazol-3-yl)-3H-benzoimidazol-5-yl]-phenyl}-methanol;
 3-(6-furan-2-yl-1H-benzoimidazol-2-yl)-2H-indazole;
 35 3-[6-(4-isopropyl-phenyl)-1H-benzoimidazol-2-yl]-2H-indazole;
 2-(1H-indazol-3-yl)-1H-benzoimidazole-5-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide;

- 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-acetyl-amino-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid methylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid isopropylamide;
[2-(1H-indazol-3-yl)-1H-benzimidazol-5-yl]-morpholin-4-yl-methanone;
- 5 [2-(1H-indazol-3-yl)-1H-benzimidazol-5-yl]-(4-methyl-piperazin-1-yl)-methanone;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid benzyl-methyl-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-nitro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-fluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2,4-difluoro-benzylamide;
- 10 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2,6-difluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-bromo-2-fluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-chloro-2-fluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-bromo-2-fluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3,4-difluoro-benzylamide;
- 15 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3,4,5-trifluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2,6-difluoro-3-methyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2,4-dichloro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-chloro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-chloro-2-methyl-benzylamide;
- 20 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-fluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2'-chloro-biphenyl-4-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (6-trifluoromethyl-pyridin-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (5-pyridin-2-yl-thiophen-2-ylmethyl)-amide;
- 25 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-imidazol-1-yl-propyl)-amide;
4-[2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxyl]-piperazine-1-carboxylic acid tert-butyl ester;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,6-difluoro-4-chloro-benzyl)amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,4-dichloro-6-fluoro-benzyl)amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-fluoro-4-chloro-benzyl)amide;
- 30 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-fluoro-4-chloro-6-methyl-benzyl)amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;
2-[5-(benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
2-[5-(3-phenyl-allyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
2-[5-(3,7-dimethyl-octa-2,6-dienyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
- 35 2-[5-(3-bromo-benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
2-[5-(3,4-dichloro-benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole;

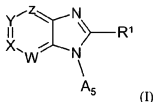
- 2-[5-(2-benzenesulfonylmethyl-benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
2-[5-(biphenyl-4-ylmethoxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
2-[5-(3-methoxy-benzyloxy)-2H-pyrazol-3-yl]-1H-benzimidazole;
isonicotinic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
5 benzoic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
3-phenyl-propionic acid 5-(1H-benzimidazol-2-yl)-1H-pyrazol-3-yl ester;
methyl 2-(1H-indazol-3-yl)-3H-benzimidazole-5-carboxylate;
5-methoxy-2-(1H-indazol-3-yl)-1H-benzimidazole; or
5-bromo 2-(1H-indazol-3-yl)-3H-benzimidazole;
- 10 or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.
159. A compound according to claim 54 which is
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(cyclohexylmethyl)amide;
15 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid N-(2-furfuryl)amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2,4-dichloro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-bromo-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-methanesulfonyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-nitro-benzylamide;
20 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-methyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (6-chloro-pyridin-3-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,3-dihydro-benzofuran-5-ylmethyl)-amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2-methylsulfonyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (benzo[b]thiophen-3-ylmethyl)-amide; 2-
25 (1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-methyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 3-chloro-benzylamide;
2-(1H-indazol-3-yl)-3H-benzimidazole-4-carboxylic acid 2-methylsulfonyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-bromo-2-fluoro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 2,4-dichloro-benzylamide;
30 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-chloro-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid 4-chloro-2-methyl-benzylamide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,6-difluoro-4-chloro-benzyl)amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2,4-dichloro-6-fluoro-benzyl)amide;
2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (3-fluoro-4-chloro-benzyl)amide;
35 2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-fluoro-4-chloro-6-methyl-benzyl)amide;
or

2-(1H-indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;
or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such
compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.

- 5 160. A compound according to claim 3 which is
2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (2-piperidin-1-yl-ethyl)-amide;
2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide;
2-(1H-Indazol-3-yl)-1H-benzimidazole-5-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide;
N-[2-(1H-Indazol-3-yl)-1H-benzimidazol-5-yl]-isobutyramide; or
- 10 N-[3-(5,6-Dimethyl-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]-2-piperidin-1-yl-acetamide;
or an N-oxide, prodrug, acid bioisostere, pharmaceutically acceptable salt or solvate of such
compound; or an N-oxide, prodrug, or acid bioisostere of such salt or solvate.

161. A compound of the of formula (I)

15



wherein

- X represents C-R² and W, Y and Z, which may be identical or different, represent CH or CR³;
- 20 R¹ represents aryl or heteroaryl chosen from pyrazolyl, triazolyl, imidazolyl, indolyl, indazolyl, thieno-
pyrazolyl, tetrahydroindazolyl, tetrahydrocyclopentapyrazolyl, dihydrofuro-pyrazolyl,
oxodihydropyridazinyl, tetrahydropyrrlopyrazolyl, oxotetrahydropyrrlopyrazolyl,
tetrahydropyranopyrazolyl, tetrahydropyridinopyrazolyl, and oxodihydropyridinopyrazolyl radicals, all
these radicals being optionally substituted with one or more radicals X¹, X² or X³ chosen from H,
- 25 halogen, haloalkyl, OH, R⁴, NO₂, CN, S(O)_nR⁴, OR⁴, NY¹Y², COR⁴, -C(=O)NY¹Y², -C(=O)OR⁴,
-C(=O)OH, -N(R⁶)C(=O)R⁴, -N(R⁶)SO₂R⁴, -N(R⁶)C(=O)NY¹Y², -N(R⁶)C(=O)OR⁴, -S(O)_nOR⁴,
-S(O)_nNY¹Y², -OC(=O)NY¹Y², -OS(O)_nR⁴, -OC(=O)R⁴ and optionally substituted thienyl;
R² and R³ are such that:
- either R² and R³, which may be identical or different, represent H, R⁴, halogen, haloalkyl, OH, NO₂,
- 30 CN, OR⁴, COR⁴, S(O)_nR⁴, -C(=O)NY¹Y², -C(=O)OR⁴, -C(=O)OH, -NY¹Y², -N(R⁶)C(=O)R⁴,
-N(R⁶)SO₂R⁴, -N(R⁶)C(=O)NY¹Y², -N(R⁶)C(=O)OR⁴, -S(O)_nOR⁴, -S(O)_nNY¹Y², -OC(=O)NY¹Y² or
-OC(=O)R⁴,

or R^2 represents H, R^4 , halogen, haloalkyl, OH, NO_2 , CN, OR^4 , COR^4 , $\text{S(O)}_n\text{R}^4$, $-\text{C(=O)NY}^1\text{Y}^2$, $-\text{C(=O)OR}^4$, $-\text{C(=O)OH}$, $-\text{NY}^1\text{Y}^2$, $-\text{N(R}^6)\text{C(=O)R}^4$, $-\text{N(R}^6)\text{SO}_2\text{R}^4$, $-\text{N(R}^6)\text{C(=O)NY}^1\text{Y}^2$, $-\text{N(R}^6)\text{C(=O)OR}^4$, $-\text{S(O)}_n\text{OR}^4$, $-\text{S(O)}_n\text{NY}^1\text{Y}^2$, $-\text{OC(=O)NY}^1\text{Y}^2$ or $-\text{OC(=O)R}^4$ and R^3 represents alkyl, haloalkyl, halogen or OR^6 ,

5

or R^2 and R^3 together form a 5- to 6-membered carbon-based ring containing one or more hetero atoms, which may be identical or different, chosen from O, N and S;

R^4 represents alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl,

10

heteroarylalkyl or arylalkyl, all these radicals being optionally substituted with one or more radicals chosen from optionally substituted aryl, halogen, alkyl, hydroxyalkyl, OH, OR^5 , $\text{C(=O)NY}^3\text{Y}^4$, NY^3Y^4 , $\text{alk-NY}^3\text{Y}^4$ and C(=O)OR^6 ;

R^5 represents alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl or heterocycloalkylalkyl;

15

Y^1 and Y^2 are such that: either Y^1 and Y^2 , which may be identical or different, represent H or optionally substituted alkyl, alkenyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, or Y^1 and Y^2 form, together with the nitrogen atom to which they are attached, a cyclic amino radical;

20

Y^3 and Y^4 are such that: either Y^3 and Y^4 , which may be identical or different, represent hydrogen, alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl or Y^3 and Y^4 form, together with the nitrogen atom to which they are attached, an optionally substituted cyclic amino radical;

25

A_3 represents H or alkyl;

R^6 is chosen from the values of R^5 ;

where

all the alkyl, or alk, which represents alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl,

30

heteroaryl and heteroarylalkyl radicals present in the above radicals furthermore being optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, cyano, alkyl, alkoxy, acylamino (NH-COalk), $-\text{C(=O)OR}^6$, acyl $-\text{C(=O)R}^6$, hydroxyalkyl, carboxyalkyl, $\text{S(O)}_n\text{-alk}$, $\text{S(O)}_n\text{-NH}_2$, $\text{S(O)}_n\text{-NH(alk)}$, $\text{S(O)}_n\text{-N(alk)}_2$, CF_3 , OCF_3 , NO_2 , arylalkoxy, aryl, heteroaryl, aryloxy, aryloxyalkyl, $-\text{C(=O)-NY}^3\text{Y}^4$ and NY^3Y^4 radicals,

35

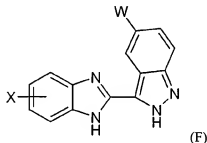
the latter radicals containing alkyl, aryl and heteroaryl being themselves optionally substituted with one or more radicals chosen from halogen atoms and alkyl radicals, free, salified or esterified carboxyl radicals and acylamino radicals NH-C(O)R^5 ,

- 5 the phenyl radicals furthermore being optionally substituted with a dioxole radical;

n represents an integer from 0 to 2,

provided that when R^1 represents an indazolyl radical

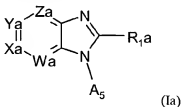
- 10 to give the compounds of formula (F) below:



with X representing H, R^2 or R^3 as defined above, then W of formula (F) necessarily represents H or unsubstituted alkyl; or the racemic, enantiomeric or diastereoisomeric isomer form of such compound,

- 15 or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

162. A compound according to claim 160 of the formula (Ia)



wherein

- 20 Xa represents $\text{C-R}^2\text{a}$; Wa , Ya and Za , which may be identical or different, represent CH or CR^3a ; R1a represents aryl or heteroaryl chosen from pyrazolyl, triazolyl and indazolyl radicals, all these radicals being optionally substituted with one or more radicals X^1a , X^2a or X^3a chosen from H, halogen, OH, R^1a , OR^1a , $\text{NY}^1\text{aY}^2\text{a}$, $\text{S(O)}_n\text{R}^4\text{a}$, $-\text{C(=O)NY}^1\text{aY}^2\text{a}$, $-\text{C(=O)OR}^4\text{a}$, $-\text{N(R}^6\text{a)C(=O)R}^4\text{a}$, $-\text{N(R}^6\text{a)SO}_2\text{R}^4\text{a}$, $-\text{N(R}^6\text{a)C(=O)NY}^1\text{aY}^2\text{a}$, $-\text{N(R}^6\text{a)C(=O)OR}^4\text{a}$, $-\text{OC(=O)NY}^1\text{aY}^2\text{a}$, $-\text{OC(=O)R}^4\text{a}$,
- 25 $-\text{OS(O)}_n\text{R}^4\text{a}$ and thienyl optionally substituted with an alkyl radical;
 R^2a and R^3a are such that:

- either R^2a and R^3a , which may be identical or different, represent H, R^4a , halogen, OH, OR^4a , $C(=O)NY^1aY^2a$, $-C(=O)OR^4a$ or $-C(=O)OH$, and R^3a represents alkyl, halogen or OR^6a , or R^2a represents H, R^4a , halogen, OH, OR^4a , $C(=O)NY^1aY^2a$, $-C(=O)OR^4a$ or $-C(=O)OH$, and R^3a represents alkyl, halogen or OR^6a ,
- 5 or R^2a and R^3a together form an $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$ ring,
 R^4a represents alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, heteroarylalkyl or arylalkyl, all these radicals being optionally substituted with one or more radicals chosen from optionally substituted aryl, halogen, alkyl, hydroxyalkyl, OH, OR^5a , $C(=O)NY^3aY^4a$, NY^3aY^4a , alk- NY^3aY^4a and $C(=O)OR^6a$,
- 10 R^5a represents alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl or heterocycloalkylalkyl, all these radicals being optionally substituted;
 Y^1a and Y^2a are such that: either Y^1a and Y^2a , which may be identical or different, represent H, alkyl, alkoxyalkyl, aryloxyalkyl, arylalkyl, heteroarylalkyl, heterocycloalkylalkyl, cycloalkyl, aryl or heteroaryl, all these radicals being optionally substituted, or Y^1a and Y^2a form, together with the
- 15 nitrogen atom to which they are attached, an optionally substituted cyclic amino radical;

Y^3a and Y^4a are such that: either Y^3a and Y^4a , which may be identical or different, represent hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl,

- 20 or Y^3a and Y^4a form, together with the nitrogen atom to which they are attached, a cyclic amino radical;

A_3 represents H or alkyl;

- 25 all the alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl radicals present in the above radicals furthermore being optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, cyano, alkyl, alkoxy, acylamino ($NH-C(O)R^6a$), $-C(=O)OR^6a$, acyl $-C(=O)R^6a$, hydroxyalkyl, carboxyalkyl, $S(O)_n$ -alk, $S(O)_n-NH_2$, $S(O)_n-NH(alk)$, $S(O)_n-N(alk)_2$, CF_3 , OCF_3 , NO_2 , arylalkoxy, aryl, heteroaryl, aryloxy, aryloxyalkyl, $-C(=O)-NY^3aY^4a$
- 30 and NY^3aY^4a radicals,

the latter radicals containing alkyl, aryl and heteroaryl themselves being optionally substituted with one or more radicals chosen from halogen atoms and alkyl radicals, alkoxy radicals, free, salified or esterified carboxyl radicals and acylamino radicals $NH-C(O)R^6a$,

35

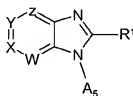
the phenyl radicals furthermore being optionally substituted with a dioxole radical;

R^6a is chosen from the values of R^5a ,

n represents an integer from 0 to 2; or

- 5 or the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

163. A compound of formula (I)



(I)

wherein

X represents $C-R^2$; and W, Y and Z, which may be identical or different, represent CH or CR^3 ;

R^1 represents aryl or heteroaryl chosen from pyrazolyl, triazolyl, imidazolyl, indolyl, indazolyl, thieno-

- 15 pyrazolyl, tetrahydroindazolyl, tetrahydrocyclopentapyrazolyl, dihydrofuropyrazolyl, oxodihydropyridazinyl, tetrahydropyrrolopyrazolyl, oxotetrahydropyrrolopyrazolyl, tetrahydropyrano-pyrazolyl, tetrahydropyridinopyrazolyl, and oxodihydro-pyridinopyrazolyl radicals, all these radicals optionally being substituted with one or more radicals X^1 , X^2 or X^3 chosen from H, halogen, haloalkyl, OH, R^4 , NO_2 , CN, $S(O)_nR^4$, OR^4 , NY^1Y^2 , COR^4 , $-C(=O)NY^1Y^2$, $-C(=O)OR^4$, $-C(=O)OH$, -
20 $N(R^6)C(=O)R^4$, $-N(R^6)SO_2R^4$, $-N(R^6)C(=O)NY^1Y^2$, $-N(R^6)C(=O)OR^4$, $-S(O)_nOR^4$, $-S(O)_nNY^1Y^2$, $-OC(=O)NY^1Y^2$, $-OS(O)_nR^4$, $-OC(=O)R^4$ and optionally substituted thienyl,

R^2 and R^3 are such that:

either R^2 and R^3 , which may be identical or different, represent H, R^4 , halogen, haloalkyl, OH, NO_2 , CN, OR^4 , COR^4 , $S(O)_nR^4$, $-C(=O)NY^1Y^2$, $-C(=O)OR^4$, $-C(=O)OH$, $-NY^1Y^2$, $-N(R^6)C(=O)R^4$,

- 25 $-N(R^6)SO_2R^4$, $-N(R^6)C(=O)NY^1Y^2$, $-N(R^6)C(=O)OR^4$, $-S(O)_nOR^4$, $-S(O)_nNY^1Y^2$, $-OC(=O)NY^1Y^2$ or $-OC(=O)R^4$

or R^2 represents H, R^4 , halogen, haloalkyl, OH, NO_2 , CN, OR^4 , COR^4 , $S(O)_nR^4$, $-C(=O)NY^1Y^2$, $-C(=O)OR^4$, $-C(=O)OH$, $-NY^1Y^2$, $-N(R^6)C(=O)R^4$, $-N(R^6)SO_2R^4$, $-N(R^6)C(=O)NY^1Y^2$, $-N(R^6)C(=O)OR^4$, $-S(O)_nOR^4$, $-S(O)_nNY^1Y^2$, $-OC(=O)NY^1Y^2$ or $-OC(=O)R^4$

- 30 and R^3 represents alkyl, haloalkyl, halogen and OR^6

or R^2 and R^3 together form a 5- to 6-membered carbon-based ring containing one or more hetero atoms, which may be identical or different, chosen from O, N and S;

R^4 represents alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, hetero-arylalkyl or arylalkyl, all these radicals being optionally substituted with one or more radicals chosen from aryl, OH, OR^5 , $C(=O)NY^3Y^4$, NY^3Y^4 and $C(=O)OR^6$;

R^3 represents alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl,

5 heteroarylalkyl and heterocycloalkylalkyl;

R^6 represents H and C1-C4 alkyl,;

n represents an integer from 0 to 2

Y^1 and Y^2 are such that: either Y^1 and Y^2 , which may be identical or different, represent H, alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl, all these radicals being optionally

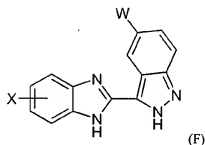
10 substituted with one or more radicals chosen from hydroxyl, $-C(=O)-NY^3Y^4$, $-C(=O)OR^6$ and NY^3Y^4 , or Y^1 and Y^2 form, together with the nitrogen atom to which they are attached, a cyclic amino radical;

Y^3 and Y^4 are such that: either Y^3 and Y^4 , which may be identical or different, represent hydrogen, alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl or Y^3 and Y^4 form, together with the nitrogen atom to which they are attached, a cyclic amino radical;

15 A_3 represents H or alkyl;

provided that when R^1 represents an indazolyl radical

to give the compound of formula (F) below:



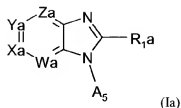
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with X representing H, R^2 or R^3 as defined above, then W of formula F necessarily represents H or unsubstituted alkyl; or

the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

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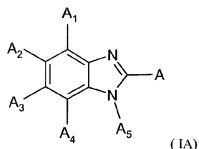
164. A compound according to claim 161 of the formula (Ia)



wherein

- Xa represents $C-R^2a$; and Wa, Ya and Za, which may be identical or different, represent CH or CR^3a ;
- 5 R^1a represents aryl or heteroaryl chosen from pyrazolyl, triazolyl and indazolyl radicals, all these radicals being optionally substituted with one or more radicals X^1a , X^2a or X^3a chosen from H, halogen, OH, R^4a , OR^4a , NY^1aY^2a , $S(O)_nR^4a$, $-C(=O)NY^1aY^2a$, $-C(=O)OR^4a$, $-N(R^6a)C(=O)R^4a$, $-N(R^6a)SO_2R^4a$, $-N(R^6a)C(=O)NY^1aY^2a$, $-N(R^6a)C(=O)OR^4a$, $-OC(=O)NY^1aY^2a$ and $-OC(=O)R^4a$, $-OS(O)_nR^4a$ and thienyl optionally substituted with an alkyl radical,
 - 10 R^2a and R^3a are such that:
either R^2a and R^3a , which may be identical or different, represent H, R^4a , halogen, OH, OR^4a , $C(=O)NY^1aY^2a$, $-C(=O)OR^4a$, or $-C(=O)OH$, and R^3a represents alkyl, halogen or OR^6a ,
or R^2a represents H, R^4a , halogen, OH, OR^4a , $C(=O)NY^1aY^2a$, $-C(=O)OR^4a$, or $-C(=O)OH$, and R^3a represents alkyl, halogen or OR^6a ,
 - 15 or R^2a and R^3a together form an $-O-CH_2-O$ or $-O-CH_2-CH_2-O-$ ring;
 R^4a represents alkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, heteroarylalkyl or arylalkyl, all these radicals being optionally substituted with one or more radicals chosen from aryl, OH, OR^5a , $C(=O)NY^3aY^4a$, NY^3aY^4a and $C(=O)OR^6a$;
 R^5a represents alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl or heterocycloalkylalkyl;
 - 20 R^6a represents H and C1-C4 alkyl;
n represents an integer from 0 to 2;
 Y^1a and Y^2a are such that: either Y^1a and Y^2a , which may be identical or different, represent H, alkyl, cycloalkyl, aryl or heteroaryl, all these radicals being optionally substituted with one or more radicals
 - 25 chosen from hydroxyl, $-C(=O)-NY^3Y^4$, $-C(=O)OR^6$ and NY^3Y^4 , or Y^1a and Y^2a form, together with the nitrogen atom to which they are attached, a cyclic amino radical;
 Y^3a and Y^4a are such that: either Y^3a and Y^4a , which may be identical or different, represent hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl, or Y^3a and Y^4a form, together with the nitrogen atom to which they are attached, a cyclic amino radical,
 - 30 A_5 represents H or alkyl; or
the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

165. A compound according to claim 161 of the formula IA



5

wherein

A represents a saturated heterocyclic radical which is either a 5- or 6-membered monocyclic radical or a bicyclic radical that is not more than 10-membered, these members being such that at least two of them represent a nitrogen atom and the others, which may be identical or different, represent a carbon member or a hetero atom member chosen from O, N and S, this heterocycle A being optionally substituted with one or more radicals XA^1 , XA^2 or XA^3 chosen from H, halogen, haloalkyl, OH, R^4 , NO_2 , CN, $S(O)_nR^4$, OR^4 , NY^1Y^2 , COR^4 , $-C(=O)NY^1Y^2$, $-C(=O)OR^4$, $-C(=O)OH$, $-N(R^6)C(=O)R^4$, $-N(R^6)SO_2R^4$, $-N(R^6)C(=O)NY^1Y^2$, $-N(R^6)C(=O)OR^4$, $-S(O)_nOR^4$, $-S(O)_nNY^1Y^2$, $-OC(=O)NY^1Y^2$, $-OS(O)_nR^4$, $-OC(=O)R^4$ and optionally substituted thienyl;

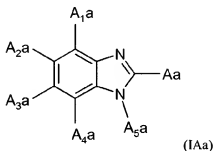
A_1 , A_2 , A_3 and A_4 , which may be identical or different, are chosen from a hydrogen atom, halogen atoms and hydroxyl, alkyl, alkenyl, alkoxy, nitro, cyano, aryl, heteroaryl and aryloxy radicals, a carboxyl radical which is free, saltified, esterified with an alkyl radical or amidated with a radical, NA^6A^7 such that either A^6 and A^7 , which may be identical or different, are chosen from a hydrogen atom and optionally substituted alkyl, alkoxyalkyl, phenoxyalkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl and heteroarylalkyl radicals, or A^6 and A^7 form, together with the nitrogen atom to which they are attached, an optionally substituted 5- or 6-membered cyclic radical, it being understood that two consecutive radicals among A_1 , A_2 , A_3 and A_4 can form, with the benzimidazole radical to which they are attached, a 5- to 6-membered carbon-based ring containing one or more hetero atoms, which may be identical or different, chosen from O, N and S;

A_5 represents a hydrogen atom or an alkyl radical;

R^6 represents hydrogen, alkyl, alkenyl, cycloalkyl, phenyl, phenylalkyl and cycloalkylalkyl,

- all the alkyl, alkenyl, aryl, heteroaryl, aryloxy, cycloalkyl and heterocycloalkyl radicals present in the above radicals being optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, cyano, alkyl, alkoxy, amino, alkylamino, dialkylamino, phenylamino, phenylalkylamino,
- 5 acylamino (NH-COR^6), $-\text{C}(=\text{O})\text{OR}^6$, acyl $-\text{C}(=\text{O})\text{R}^6$, hydroxyalkyl, carboxyalkyl, phenoxyalkyl, $\text{S}(\text{O})_n\text{-alk}$, $\text{S}(\text{O})_n\text{-NH}_2$, $\text{S}(\text{O})_n\text{-NH(alk)}$, $\text{S}(\text{O})_n\text{-N(alk)}_2$, CF_3 , OCF_3 , NO_2 , CN , phenyl, itself optionally substituted with one or more halogen atoms, thienyl, phenoxy, phenylalkoxy, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{-NH(alk)}$ and $\text{C}(=\text{O})\text{-N(alk)}_2$ radicals,
- all the above alkyl, alkenyl, alkoxy and alkylthio radicals being linear or branched and containing not
- 10 more than 4 carbon atoms,
- all the phenyl radicals of the above radicals furthermore being optionally substituted with a dioxole radical;
- n represents an integer from 0 to 2; or
- 15 the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

166. A compound according to claim 161 of the formula (IAa):



- 20 in which Aa represents a pyrazolyl, triazolyl or indazolyl radical, this heterocycle Aa being optionally substituted with one or more radicals XA^1 , XA^2 or XA^3 chosen from H, halogen, haloalkyl, OH, R^4 , NO_2 , CN , $\text{S}(\text{O})_n\text{R}^4$, OR^4 , NY^1Y^2 , COR^4 , $-\text{C}(=\text{O})\text{NY}^1\text{Y}^2$, $-\text{C}(=\text{O})\text{OR}^4$, $-\text{C}(=\text{O})\text{OH}$, $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{R}^4$, $-\text{N}(\text{R}^6)\text{SO}_2\text{R}^4$, $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{NY}^1\text{Y}^2$, $-\text{N}(\text{R}^6)\text{C}(=\text{O})\text{OR}^4$, $-\text{S}(\text{O})_n\text{OR}^4$, $-\text{S}(\text{O})_n\text{NY}^1\text{Y}^2$, $-\text{OC}(=\text{O})\text{NY}^1\text{Y}^2$, $-\text{OS}(\text{O})_n\text{R}^4$, $-\text{OC}(=\text{O})\text{R}^4$ and optionally substituted thienyl;

A_{1a}, A_{2a}, A_{3a} and A_{4a}, which may be identical or different, are chosen from a hydrogen atom, halogen atoms, hydroxyl, alkyl, alkoxy, nitro, cyano, phenyl and phenoxy radicals, and a carboxyl radical which is free, salified, esterified with an alkyl radical or amidated with a

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radical NA^6aA^7a such that either A^6a and A^7a , which may be identical or different, are chosen from a hydrogen atom and alkyl, phenyl, phenylalkyl, cycloalkylalkyl, cycloalkyl, furylalkyl, thienylalkyl and pyridylalkyl radicals, or A^6a and A^7a form, together with the nitrogen atom to which they are attached, a pyrrolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, morpholino or piperazinyl radical optionally substituted on the second nitrogen atom with an alkyl or phenyl radical, which are themselves optionally substituted,

it being understood that two consecutive radicals from among A_1a , A_2a , A_3a and A_4a may form, with the benzimidazole radical to which they are attached, an optionally substituted 5- to 6-membered carbon-based ring containing one or two oxygen atoms,

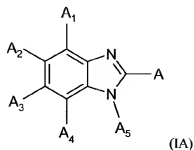
A_5a represents a hydrogen atom or an alkyl radical,

the phenyl and phenoxy radicals above being optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, amino, alkylamino, dialkylamino, phenylamino, phenylalkylamino, free, salified or esterified carboxyl, and dioxole radicals;

all the alkyl, alkoxy and alkylthio radicals above being linear or branched and containing not more than 6 carbon atoms; or

the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

167. A compound according to claim 161 of the formula IA

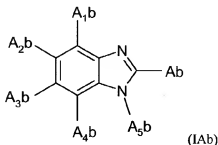


wherein

- A represents a saturated heterocyclic radical which is either a 5- or 6-membered monocyclic radical or a bicyclic radical that is not more than 10-membered, these members being such that at least two of them represent a nitrogen atom and the others, which may be identical or different, represent a carbon member or a hetero atom member chosen from O, N and S, this heterocycle A optionally being
- 5 substituted with one or more radicals XA^1 , XA^2 or XA^3 chosen from halogen atoms, alkyl, alkoxy or alkylthio radicals or thienyl radicals optionally substituted with an alkyl radical;

- A_1 , A_2 , A_3 and A_4 , which may be identical or different, are chosen from a hydrogen atom, halogen atoms and hydroxyl, alkyl, alkoxy, nitro, cyano, phenyl and phenoxy radicals, a carboxyl radical which
- 10 is free, salified, esterified with an alkyl radical or amidated with a radical NA^6A^7 such that either A^6 and A^7 , which may be identical or different, are chosen from a hydrogen atom and alkyl, phenyl, phenylalkyl, cycloalkylalkyl, cycloalkyl and heteroarylalkyl radicals, or A^6 and A^7 form, together with the nitrogen atom to which they are attached, a 5- or 6-membered cyclic radical,
- 15 it being understood that two consecutive radicals among A_1 , A_2 , A_3 and A_4 can form, with the benzimidazole radical to which they are attached, a 5- to 6-membered carbon-based ring containing one or more hetero atoms, which may be identical or different, chosen from O, N and S;
- A_5 represents a hydrogen atom or an alkyl radical;
- all the phenyl, phenoxy, cycloalkyl and heteroarylalkyl radicals above being optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, cyano, trifluoromethyl,
- 20 trifluoromethoxy, alkyl, alkoxy, amino, alkylamino, dialkylamino, phenylamino, phenylalkylamino, free, salified or esterified carboxyl, and dioxole radicals;
- all the alkyl, alkoxy and alkylthio radicals above being linear or branched and containing not more than 6 carbon atoms; or
- the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt
- 25 with a mineral or an organic acid or with a mineral base of such compound.

168. A compound according to claim 161 of formula IAb



wherein

Ab represents a pyrazolyl or indazolyl radical optionally substituted with one or two radicals chosen from halogen atoms and OH, alkyl, alkenyl, $-OR^6b$ including alkoxy, $-COR^6b$, $-O-COR^6b$, $-OS(O)_nR^6b$, $-O(CH_2)_n-CO-R^6b$, phenyl, phenylalkyl, CF_3 , OCF_3 , NO_2 , CN, NY^1bY^2b , $-NH-C(=O)NY^1bY^2b$,
 5 acylamino ($NH-CO-R^6b$), $S(O)_nalk$, $S(O)_n-NY^1bY^2b$, $-C(=O)-NY^1bY^2b$, $-C(=O)OR^6b$, $-NH-C(=O)R^6b$, $-NH-S(O)_nR^6b$, $-NH-C(=O)OR^6b$, $-N(R^6b)C(=O)NY^1bY^2b$, $-OC(=O)NY^1bY^2b$ and thienyl radicals, all these radicals being optionally substituted,

with NY^1bY^2b such that either Y^1b and Y^2b , which may be identical or different, are chosen from

- 10 hydrogen and optionally substituted alkyl, cycloalkyl, cycloalkylalkyl, phenyl, naphthyl, phenoxy, phenylalkyl, phenylalkylthio and naphthylalkyl or Y^1b and Y^2b form, together with the nitrogen atom to which they are attached, a piperidyl, hexahydrofuran, morpholinyl or morpholinylalkyl radical;

- 15 A_1b , A_2b , A_3b and A_4b , which may be identical or different, are chosen from a hydrogen atom, halogen atoms, hydroxyl, alkyl, alkenyl, $-OR^6b$ including alkoxy, $-CO-R^6b$, $-O-COR^6b$, $-OS(O)_nR^6b$, $-O(CH_2)_n-CO-R^6b$, nitro, cyano, furyl, thienyl, benzothienyl, naphthyl, thianthrenyl, phenyl and phenoxy radicals and a carboxyl radical which is free, salified, esterified with an alkyl radical or amidated with a radical NA^6bA^7b such that either A^6b and A^7b , which may be identical or different, are chosen from hydrogen and alkyl, alkoxyalkyl,
 20 phenoxyalkyl, phenyl, phenylalkyl, cycloalkylalkyl, cycloalkyl, furylalkyl, naphthylalkyl, thienylalkyl, piperidylalkyl, pyridylalkyl, benzothienylalkyl, pyrazolylalkyl, dihydrobenzofuranylalkyl, hexahydropyranalkyl, ethylenedioxyphenylalkyl and benzimidazolylalkyl radicals, all these radicals being optionally substituted, or A^6b and A^7b form, together with the nitrogen atom to which they are attached, a pyrrolidinyl, morpholino or
 25 piperazinyl radical, the piperazinyl radical being optionally substituted on the second nitrogen atom with an alkyl radical itself optionally substituted,

it being understood that two consecutive radicals among A_1b , A_2b , A_3b and A_4b can form, with the benzimidazole radical to which they are attached, an optionally substituted

- 30 4,5-ethylenedioxybenzimidazole radical or an optionally substituted
 4,5-methylenedioxybenzimidazole radical;
 A_5b represents a hydrogen atom;

all the above radicals containing alkyl, alkenyl, phenyl, phenoxy, furyl, thienyl, piperidyl, pyridyl,
 35 pyrazolyl and benzimidazolyl being optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, cyano, alkyl, alkoxy, amino, alkylamino, dialkylamino, phenylamino,

phenylalkylamino, acylamino ($\text{NH-COR}^6\text{b}$), $-\text{C}(=\text{O})\text{OR}^6\text{b}$, acyl $-\text{C}(=\text{O})\text{R}^6\text{b}$, hydroxyalkyl, carboxyalkyl, phenoxyalkyl, $\text{S}(\text{O})_n\text{-alk}$, $\text{S}(\text{O})_n\text{-NH}_2$, $\text{S}(\text{O})_n\text{-NH(alk)}$, $\text{S}(\text{O})_n\text{-N(alk)}_2$, CF_3 , OCF_3 , NO_2 , CN , phenyl, itself optionally substituted with one or more halogen atoms, thienyl, phenoxy, phenylalkoxy, $-\text{C}(=\text{O})\text{-NH}_2$, $-\text{C}(=\text{O})\text{-NH(alk)}$ and $\text{C}(=\text{O})\text{-N(alk)}_2$ radicals,

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with n representing an integer from 0 to 2,

and R^6b representing hydrogen, alkyl, alkenyl, cycloalkyl, phenyl, pyridyl, thienyl, naphthyl, isoxazole, adamantlyl, quinoline, quinolone, dihydroquinolone, $-\text{NH-phenyl}$, phenylalkyl or cycloalkylalkyl, all

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these radicals being optionally substituted with a morpholino, piperidyl or phenyl radical itself optionally substituted with one or more radicals chosen from halogen atoms and the cyano, CF_3 , OCF_3 , alkyl, phenyl- $\text{S}(\text{O})_n\text{-alk-phenyl}$, alkoxy, NH_2 , NHalk , N(alk)_2 , SO_2NH_2 , SO_2Nalk or $\text{SO}_2\text{N(alk)}_2$ radical,

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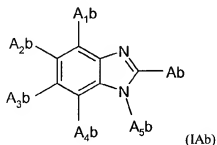
all the alkyl, alkenyl, alkoxy and alkylthio radicals above being linear or branched and containing not more than 10 carbon atoms,

all the phenyl radicals of the above radicals furthermore being optionally substituted with a dioxole radical; or

the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

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169. A compound according to claim 161 of the formula IAb



wherein

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Ab represents a pyrazolyl or indazolyl radical optionally substituted with one or two radicals chosen from halogen atoms and OH, alkyl, alkenyl, alkoxy, phenyl, phenylalkyl, CF_3 , OCF_3 , NO_2 , CN , $\text{NY}^1\text{bY}^2\text{b}$, $-\text{NH-C}(=\text{O})\text{NY}^1\text{bY}^2\text{b}$, acylamino ($\text{NH-CO-R}^6\text{b}$), $\text{S}(\text{O})_n\text{-alk}$, $\text{S}(\text{O})_n\text{-NY}^1\text{bY}^2\text{b}$, $-\text{C}(=\text{O})\text{-NY}^1\text{bY}^2\text{b}$, $-\text{C}(=\text{O})\text{OR}^6\text{b}$, $-\text{NH-C}(=\text{O})\text{R}^6\text{b}$, $-\text{NH-S}(\text{O})_n\text{R}^6\text{b}$, $-\text{NH-C}(=\text{O})\text{OR}^6\text{b}$, $-\text{N(R}^6\text{b})\text{C}(=\text{O})\text{NY}^1\text{bY}^2\text{b}$, $-\text{OC}(=\text{O})\text{NY}^1\text{bY}^2\text{b}$ and thienyl radicals which are optionally substituted,

with NY^1bY^2b such that either Y^1b and Y^2b , which may be identical or different, are chosen from hydrogen and optionally substituted alkyl, cycloalkyl, cycloalkylalkyl, phenyl, naphthyl, phenoxy, phenylalkyl, phenylalkylthio and naphthylalkyl or Y^1b and Y^2b form, together with the nitrogen atom to which they are attached, a piperidyl, hexahydrofuran, morpholinyl or morpholinylalkyl radical;

- 5 A_1b, A_2b, A_3b and A_4b , which may be identical or different, are chosen from a hydrogen atom, halogen atoms, hydroxyl, alkyl, alkenyl, alkoxy, nitro, cyano, furyl, thienyl, benzothienyl, naphthyl, thianthrenyl, phenyl and phenoxy radicals and a carboxyl radical which is free, salfified, esterified with an alkyl radical or amidated with a radical NA^6bA^7b such that either A^6b and A^7b , which may be identical or different, are chosen from hydrogen and alkyl,
- 10 alkoxyalkyl, phenoxyalkyl, phenyl, phenylalkyl, cycloalkylalkyl, cycloalkyl, furylalkyl, naphthylalkyl, thienylalkyl, piperidylalkyl, pyridylalkyl, benzothienylalkyl, pyrazolylalkyl, dihydrobenzofuranylalkyl, hexahydropyranalkyl, ethylenedioxyphenylalkyl and benzimidazolylalkyl radicals, all these radicals being optionally substituted, or A^6b and A^7b form, together with the nitrogen atom to which they are attached, a pyrrolidinyl, morpholino or
- 15 piperazinyl radical, the piperazinyl radical being optionally substituted on the second nitrogen atom with an alkyl radical itself optionally substituted,

it being understood that two consecutive radicals among A_1b, A_2b, A_3b and A_4b can form, with the benzimidazole radical to which they are attached, an optionally substituted

- 20 4,5-ethylenedioxybenzimidazole radical or an optionally substituted

4,5-methylenedioxybenzimidazole radical;

A_3b represents a hydrogen atom;

all the above radicals containing alkyl, alkenyl, phenyl, phenoxy, furyl, thienyl, piperidyl, pyridyl, pyrazolyl and benzimidazolyl being optionally substituted with one or more radicals chosen from

25 halogen atoms and hydroxyl, cyano, alkyl, alkoxy, amino, alkylamino, dialkylamino, phenylamino, phenylalkylamino, acylamino ($NH-COR^6b$), $-C(=O)OR^6b$, acyl $-C(=O)R^6b$, hydroxyalkyl, carboxyalkyl, phenoxyalkyl, $S(O)_n-alk$, $S(O)_n-NH_2$, $S(O)_n-NH(alk)$, $S(O)_n-N(alk)_2$, CF_3 , OCF_3 , NO_2 , CN, phenyl, itself optionally substituted with one or more halogen atoms, thienyl, phenoxy, phenylalkoxy, $-C(=O)-NH_2$, $-C(=O)-NH(alk)$ or $C(=O)-N(alk)_2$ radicals;

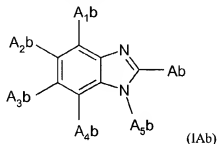
- 30 with n representing an integer from 0 to 2,

and R^6b representing hydrogen, alkyl, alkenyl, cycloalkyl, phenyl, phenylalkyl or cycloalkylalkyl, all the alkyl, alkenyl, alkoxy and alkylthio radicals above being linear or branched and containing not more than 10 carbon atoms,

- 35 all the phenyl radicals of the above radicals furthermore being optionally substituted with a dioxide radical; or

the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

170. A compound according to claim 161 of the formula IAb



wherein

Ab represents a pyrazolyl radical substituted with one or two radicals such that one is chosen from hydrogen, halogen atoms and alkyl, alkynyl, $-\text{COR}^{\text{c}}\text{b}$, phenyl, phenylalkyl, CF_3 , NO_2 , CN, $\text{NY}^1\text{bY}^2\text{b}$, $-\text{NH}-\text{C}(=\text{O})\text{NY}^1\text{bY}^2\text{b}$, $\text{NH}-\text{CO}-\text{R}^{\text{c}}\text{b}$, $\text{S}(\text{O})_n\text{-alk}$, $\text{S}(\text{O})_n\text{-NY}^1\text{bY}^2\text{b}$, $-\text{C}(=\text{O})\text{-NY}^1\text{bY}^2\text{b}$, $-\text{C}(=\text{O})\text{OR}^{\text{c}}\text{b}$, $-\text{NH}-\text{C}(=\text{O})\text{R}^{\text{c}}\text{b}$, $-\text{NH}-\text{S}(\text{O})_n\text{R}^{\text{c}}\text{b}$, $-\text{NH}-\text{C}(=\text{O})\text{OR}^{\text{c}}\text{b}$, $-\text{N}(\text{R}^{\text{c}}\text{b})\text{C}(=\text{O})\text{NY}^1\text{bY}^2\text{b}$ and thienyl radicals, all these radicals being optionally substituted,

and the other is chosen from OH , $-\text{OR}^{\text{c}}\text{b}$, $-\text{O}-\text{COR}^{\text{c}}\text{b}$, $-\text{OS}(\text{O})_n\text{R}^{\text{c}}\text{b}$, $-\text{O}(\text{CH}_2)_n\text{-CO}-\text{R}^{\text{c}}\text{b}$ and

$-\text{OC}(=\text{O})\text{NY}^1\text{bY}^2\text{b}$ radicals, all these radicals being optionally substituted,

with $\text{NY}^1\text{bY}^2\text{b}$ such that Y^1b and Y^2b , which may be identical or different, are chosen from hydrogen and optionally substituted alkyl, cycloalkyl, cycloalkylalkyl, phenyl, naphthyl, phenoxy, phenylalkyl, phenylalkylthio and naphthylalkyl or Y^1b and Y^2b form, together with the nitrogen atom to which they are attached, a piperidyl, hexahydrofuran, morpholinyl or morpholinylalkyl radical;

A_1b , A_2b , A_3b and A_4b , which may be identical or different, are such that two of them represent hydrogen and the other two, which may be identical or different, are chosen from a hydrogen atom, halogen atoms, hydroxyl, alkyl, alkenyl, $-\text{OR}^{\text{c}}\text{b}$ (including alkoxy), $-\text{CO}-\text{R}^{\text{c}}\text{b}$, $-\text{O}-\text{COR}^{\text{c}}\text{b}$, $-\text{OS}(\text{O})_n\text{R}^{\text{c}}\text{b}$, $-\text{O}(\text{CH}_2)_n\text{-CO}-\text{R}^{\text{c}}\text{b}$, nitro, cyano, furyl, thienyl, benzothienyl, naphthyl,

thianthrenyl, phenyl and phenoxy radicals and a carboxyl radical which is free, salified, esterified with an alkyl radical or amidated with a radical $\text{NA}^{\text{c}}\text{bA}^{\text{c}}\text{b}$ such that either $\text{A}^{\text{c}}\text{b}$ and $\text{A}^{\text{c}}\text{b}$, which may be identical or different, are chosen from hydrogen and alkyl, alkoxyalkyl, phenoxyalkyl, phenyl, phenylalkyl, cycloalkylalkyl, cycloalkyl, furylalkyl, naphthylalkyl, thienylalkyl, piperidylalkyl, pyridylalkyl, benzothienylalkyl, pyrazolylalkyl,

dihydrobenzofuranylalkyl, hexahydropyranalkyl, ethylenedioxyphenylalkyl and benz-

imidazolylalkyl radicals, all these radicals being optionally substituted, or A^6b and A^7b form, together with the nitrogen atom to which they are attached, a pyrrolidinyl, morpholino or piperazinyl radical, the piperazinyl radical being optionally substituted on the second nitrogen atom with an alkyl radical itself optionally substituted;

5 A_3b represents a hydrogen atom,

all the above radicals containing alkyl, alkenyl, phenyl, phenoxy, furyl, thienyl, piperidyl, pyridyl, pyrazolyl and benzimidazolyl being optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, cyano, alkyl, alkoxy, amino, alkylamino, dialkylamino, phenylamino, phenylalkylamino, acylamino ($NH-COR^6b$), $-C(=O)OR^6b$, acyl $-C(=O)R^6b$, hydroxyalkyl,

10 carboxyalkyl, phenoxyalkyl, $S(O)_n-alk$, $S(O)_n-NH_2$, $S(O)_n-NH(alk)$, $S(O)_n-N(alk)_2$, CF_3 , OCF_3 , NO_2 , CN , phenyl, itself optionally substituted with one or more halogen atoms, thienyl, phenoxy, phenylalkoxy, $-C(=O)-NH_2$, $-C(=O)-NH(alk)$ and $C(=O)-N(alk)_2$ radicals;

with n representing an integer from 0 to 2;

and R^6b representing hydrogen, alkyl, alkenyl, cycloalkyl, phenyl, pyridyl, thienyl, naphthyl, isoxazole,

15 adamantyl, quinoline, quinolone, dihydroquinolone, $-NH$ -phenyl, phenylalkyl and cycloalkylalkyl, all these radicals being optionally substituted with a morpholino, piperidyl or phenyl radical itself optionally substituted with one or more radicals chosen from halogen atoms and the cyano, CF_3 , OCF_3 , alkyl, phenyl- $S(O)_n-alk$ -phenyl, alkoxy, NH_2 , $NHalk$, $N(alk)_2$, SO_2NH_2 , SO_2Nalk or $SO_2N(alk)_2$ radical,

all the alkyl, alkenyl, alkoxy and alkylthio radicals above being linear or branched and

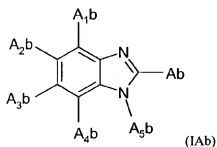
20 containing not more than 10 carbon atoms,

all the phenyl radicals of the above radicals furthermore being optionally substituted with a dioxole radical; or

the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

25

171. A compound according to claim 161 of the formula IAb



30 wherein

Ab represents a pyrazolyl or indazolyl radical optionally substituted with one or more radicals chosen from halogen atoms and alkyl, alkoxy and thienyl radicals;

- A₁b, A₂b, A₃b and A₄b, which may be identical or different, are chosen from a hydrogen atom; halogen atom; hydroxyl, alkyl, alkenyl optionally substituted with phenyl itself optionally substituted with one or more halogen atoms, alkoxy, nitro, cyano, furyl, thienyl optionally substituted with acyl COalk, benzothienyl, naphthyl, thianthrenyl, phenyl and phenoxy which are optionally substituted; and a carboxyl radical which is free, salified, esterified with an alkyl radical or amidated with a radical NA⁶bA⁷b such that either A⁶b and A⁷b, which may be identical or different, are chosen from hydrogen, alkyl, alkoxyalkyl containing not more than 6 carbon atoms, phenoxyalkyl optionally substituted with acylamino NH-C(O)alk, phenyl, optionally substituted phenylalkyl, cycloalkylalkyl, cycloalkyl, furylalkyl optionally substituted with one or more alkyl radicals, naphthylalkyl, thienylalkyl optionally substituted with alkyl or thienyl, piperidylalkyl optionally substituted with a carboxyl radical which is free, salified or esterified with an alkyl radical, pyridylalkyl optionally substituted with one or more radicals chosen from halogen and CF₃, benzothienylalkyl, pyrazolylalkyl optionally substituted with one or more alkyl radicals, dihydrobenzofuranylalkyl, hexahydropyranylalkyl, ethylenedioxyphenylalkyl, and benzimidazolylalkyl optionally substituted with one or more alkyl radicals;
- or A⁶b and A⁷b form, together with the nitrogen atom to which they are attached, a pyrrolidinyl, morpholino or piperazinyl radical, the piperazinyl radical being optionally substituted on the second nitrogen atom with an alkyl radical, it being understood that two consecutive radicals among A₁b, A₂b, A₃b and A₄b can form, with the benzimidazole radical to which they are attached, an optionally substituted 4,5-ethylenedioxybenzimidazole radical or an optionally substituted 4,5-methylenedioxybenzimidazole radical;
- A₅a represents a hydrogen atom; the phenyl, phenoxy and phenylalkyl radicals above being optionally substituted with one or more radicals chosen from halogen atoms, hydroxyl, cyano, alkyl, alkoxy, amino, alkylamino, dialkylamino, phenylamino, phenylalkylamino and NH-COalk radicals, a carboxyl radical which is free, salified or esterified with an alkyl radical, and hydroxyalkyl, carboxyalkyl, phenoxyalkyl, alkylthio, SO₂alk, SO₂NH₂, SO₂-NH(alk), SO₂-N(alk)₂, CF₃, OCF₃, NO₂, CN, phenyl, itself optionally substituted with one or more halogen atoms, thienyl, phenoxy, phenylalkoxy, -C(=O)-NH₂, -C(=O)-NH(alk), C(=O)-N(alk)₂ and C(O)CH₃ radicals;
- all the alkyl or alk, alkenyl, alkoxy and alkylthio radicals above being linear or branched and containing not more than 4 carbon atoms,

all the phenyl radicals of the above radicals furthermore being optionally substituted with a dioxole radical; or

the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

5

172. A compound according to any one of claims 168, 169, 170 or 171 wherein when one of A_1b , A_2b , A_3b and A_4b represents a carboxyl radical amidated with a radical NA^6bA^7b , then either one of A^6b and A^7b represents a hydrogen atom or an alkyl radical and the other of A^6b and A^7b is chosen from the values defined for A^6b and A^7b , or A^6b and A^7b form, together with the nitrogen atom to which they are attached, a 5- or 6-membered cyclic radical; or

10

the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

15

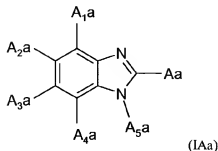
173. A compound according to claim 161 wherein X, W, Y and Z are such that two or three of them represent CH and the others are chosen from CR^2 and CR^3 and, when two of them represent CH and CR^2 and CR^3 are adjacent to each other, can form a dioxole radical; or the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

20

174. A compound according to claim 165 or claim 167 wherein A_1 , A_2 , A_3 and A_4 are such that two or three of them represent a hydrogen atom and, when two of them represent a hydrogen atom and the other two are on adjacent carbons, can form a dioxole radical; or the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

25

175. A compound according to claim 161 of the formula (IAa)



30

wherein

Aa represents a pyrazolyl, triazolyl or indazolyl radical, this heterocycle Aa being optionally substituted with one or more radicals XA^1 , XA^2 or XA^3 chosen from halogen atoms, alkyl, alkoxy, alkylthio radicals and thienyl radicals optionally substituted with an alkyl radical,

- 5 A_{1a} , A_{2a} , A_{3a} and A_{4a} , which may be identical or different, are chosen from a hydrogen atom, halogen atoms, hydroxyl, alkyl, alkoxy, nitro, cyano, phenyl and phenoxy radicals, and a carboxyl radical which is free, salified, esterified with an alkyl radical or amidated with a radical NA^6aA^7a such that either A^6a and A^7a , which may be identical or different, are chosen from a hydrogen atom and alkyl, phenyl, phenylalkyl, cycloalkylalkyl, cycloalkyl, furylalkyl, thienylalkyl and pyridylalkyl radicals, or A^6a and
- 10 A^7a form, together with the nitrogen atom to which they are attached, a pyrrolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, morpholino or piperazinyl radical optionally substituted on the second nitrogen atom with an alkyl or phenyl radical, which are themselves optionally substituted, it being understood that two consecutive radicals from among A_{1a} , A_{2a} , A_{3a} and A_{4a} may form, with the benzimidazole radical to which they are attached, an optionally substituted 5- to 6-membered
- 15 carbon-based ring containing one or two oxygen atoms,

A_{5a} represents a hydrogen atom or an alkyl radical,

the phenyl and phenoxy radicals above being optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, cyano, trifluoromethyl, trifluoromethoxy, alkyl, alkoxy, amino, alkylamino, dialkylamino, phenylamino, phenylalkylamino, free, salified or esterified carboxyl, and
- 20 dioxole radicals,

all the alkyl, alkoxy and alkylthio radicals above being linear or branched and containing not more than 6 carbon atoms; or

the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

25

176. A compound according to claim 161 wherein R^1 represents a pyrazolyl or indazolyl radical.

177. A compound according to claim 166 or claim 175 wherein

Aa represents an optionally substituted pyrazolyl or an optionally substituted indazolyl radical,

- 30 A_{1a} , A_{2a} , A_{3a} and A_{4a} are chosen from the following values:

A_{1a} represents hydrogen or carboxyl or forms a ring with the adjacent member A_{2a} ;

A_{2a} represents hydrogen or carboxyl or forms a ring with the adjacent member A_{3a} ;

A_{3a} represents a carboxyl radical that is free, salified, esterified with an optionally substituted alkyl radical or an amidated carboxyl;

35

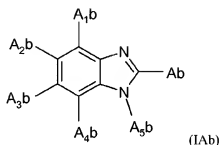
A_{2a} and A_{3a} represent two optionally substituted alkyl radicals; and

A_{3a} represents hydrogen; or

the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

5

178. A compound according to claim 161 of the formula (IAb):



10

wherein

Ab represents a pyrazolyl or indazolyl radical optionally substituted with one or more radicals chosen from halogen atoms and alkyl, alkoxy and thienyl radicals,

- 15 A_{1b}, A_{2b}, A_{3b} and A_{4b}, which may be identical or different, are chosen from a hydrogen atom, halogen atoms, hydroxyl, alkyl and alkoxy, nitro, cyano, phenyl and phenoxy radicals, and a carboxyl radical that is free, salified, esterified with an alkyl radical or amidated with a radical NA^{6b}A^{7b} such that either A^{6b} and A^{7b}, which may be identical or different, are chosen from alkyl, phenyl, phenylalkyl, cycloalkylalkyl, cycloalkyl and furylalkyl radicals, or A^{6b} and A^{7b} form, together with the nitrogen atom to which they are attached, a pyrrolidinyl, morpholino or piperazinyl radical optionally
- 20 substituted on the second nitrogen atom with an alkyl radical,

it being understood that two consecutive radicals from among A_{1b}, A_{2b}, A_{3b} and A_{4b} may form, with the benzimidazole radical to which they are attached, an optionally substituted

4,5-ethylenedioxybenzimidazole radical or 4,5-methylenedioxybenzimidazole radical,

A_{5b} represents a hydrogen atom,

- 25 the phenyl and phenoxy radicals above being optionally substituted with one or more radicals chosen from halogen atoms and hydroxyl, cyano, alkyl, alkoxy, amino, alkylamino, dialkylamino, phenylamino, phenylalkylamino and free, salified or esterified carboxyl radicals, all the alkyl, alkoxy and alkylthio radicals above being linear or branched and containing not more than 4 carbon atoms; or

the racemic, enantiomeric or diastereoisomeric isomer form of such compound, or the addition salt with a mineral or an organic acid or with a mineral base of such compound.

179. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound
5 according to any one of claims 3 to 178, together with one or more pharmaceutically acceptable carriers or excipients.
180. A method of treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of the catalytic activity of Syk comprising
10 administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.
181. A method of treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of the catalytic activity of Syk comprising
15 administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.
182. A method of treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of the catalytic activity of KDR comprising
20 administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.
183. A method of treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of the catalytic activity of KDR comprising
25 administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.
184. A method of treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of the catalytic activity of tie2 comprising
30 administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.
185. A method of treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of the catalytic activity of tie2 comprising
35 administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.

186. A method of treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of the catalytic activity of ITK comprising administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.
187. A method of treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of the catalytic activity of ITK comprising administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.
188. A method of treating inflammatory disease in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.
189. A method of treating inflammatory disease in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.
190. A method of treating cancer in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.
191. A method of treating cancer in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.
192. A method of treating Chronic Obstructive Pulmonary Disease, in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.
193. A method of treating Chronic Obstructive Pulmonary Disease, in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.
194. A method of treating asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, silicosis, pulmonary sarcoidosis,

rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis, acute and chronic urticaria, cutaneous and systemic anaphylaxis, endotoxemia, sepsis, septic shock, endotoxic shock, gram negative sepsis, diabetes, multiple sclerosis, systemic lupus erythromatosis, viral infections, bacterial infections, parasitic infections, graft vs. host disease, organ transplant rejection, reperfusion injury, Crohn's disease or ulcerative colitis, in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.

195. A method of treating asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, silicosis, pulmonary sarcoidosis, rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis, acute and chronic urticaria, cutaneous and systemic anaphylaxis, endotoxemia, sepsis, septic shock, endotoxic shock, gram negative sepsis, diabetes, multiple sclerosis, systemic lupus erythromatosis, viral infections, bacterial infections, parasitic infections, graft vs. host disease, organ transplant rejection, reperfusion injury, Crohn's disease or ulcerative colitis, in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.

196. A method of treating cancers, atherosclerosis, degenerative muscle diseases, obesity, congestive heart failure, Parkinson's, depression, schizophrenia, stroke, head trauma, spinal cord injury, Alzheimer's, neuropathic pain syndrome, amyotrophic lateral sclerosis, cachexia, osteoporosis or fibrotic diseases of the viscera, in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.

197. A method of treating cancers, atherosclerosis, degenerative muscle diseases, obesity, congestive heart failure, Parkinson's, depression, schizophrenia, stroke, head trauma, spinal cord injury, Alzheimer's, neuropathic pain syndrome, amyotrophic lateral sclerosis, cachexia, osteoporosis or fibrotic diseases of the viscera, in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.

198. A method of treating asthma, atopic dermatitis, psoriasis, dematitis herpetiformis, eczema, necrotizing and cutaneous vasculitis, bullous disease, acute and chronic urticaria, allergic rhinitis or allergic conjunctivitis, arthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis and osteoarthritis, Chronic Obstructive Pulmonary Disease, adult respiratory distress syndrome, silicosis, pulmonary sarcoidosis, acute synovitis, autoimmune diabetes, autoimmune encephalomyelitis, colitis, atherosclerosis, peripheral vascular disease,

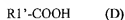
cardiovascular disease, cutaneous and systemic anaphylaxis, endotoxemia, sepsis, septic shock, endotoxic shock, gram negative sepsis, diabetes, multiple sclerosis, restenosis, myocarditis, B cell lymphomas, systemic lupus erythematosus, viral infections, bacterial infections, parasitic infections, graft v host disease and other transplant associated rejection events, reperfusion injury, Crohn's disease, ulcerative colitis, cancers, tumours, atherosclerosis, degenerative muscle diseases, obesity, congestive heart failure, Parkinson's, depression, schizophrenia, stroke, head trauma, spinal cord injury, Alzheimer's, neuropathic pain syndrome, amyotrophic lateral sclerosis, cachexia, osteoporosis, fibrotic diseases of the viscera, or inflammatory bowel disease, in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.

199. A method of treating asthma, atopic dermatitis, psoriasis, dermatitis herpetiformis, eczema, necrotizing and cutaneous vasculitis, bullous disease, acute and chronic urticaria, allergic rhinitis or allergic conjunctivitis, arthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis and osteoarthritis, Chronic Obstructive Pulmonary Disease, adult respiratory distress syndrome, silicosis, pulmonary sarcoidosis, acute synovitis, autoimmune diabetes, autoimmune encephalomyelitis, colitis, atherosclerosis, peripheral vascular disease, cardiovascular disease, cutaneous and systemic anaphylaxis, endotoxemia, sepsis, septic shock, endotoxic shock, gram negative sepsis, diabetes, multiple sclerosis, restenosis, myocarditis, B cell lymphomas, systemic lupus erythematosus, viral infections, bacterial infections, parasitic infections, graft v host disease and other transplant associated rejection events, reperfusion injury, Crohn's disease, ulcerative colitis, cancers, tumours, atherosclerosis, degenerative muscle diseases, obesity, congestive heart failure, Parkinson's, depression, schizophrenia, stroke, head trauma, spinal cord injury, Alzheimer's, neuropathic pain syndrome, amyotrophic lateral sclerosis, cachexia, osteoporosis, fibrotic diseases of the viscera, or inflammatory bowel disease, in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.

200. A method of inhibiting angiogenesis in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.

201. A method of inhibiting angiogenesis in a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.

202. A method according to claim 190 or claim 191 wherein the cancer being treated is colorectal, prostate, breast, thyroid, skin, colon or lung cancer.
203. A method of treating asthma in a patient in need thereof comprising administering to said
5 patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.
204. A method of treating asthma in a patient in need thereof comprising administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.
- 10 205. A method of treating psoriasis in a patient in need thereof comprising administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.
206. A method of treating psoriasis in a patient in need thereof comprising administering to said
15 patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.
207. A method of treating joint inflammation in a patient in need thereof comprising administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to
20 178.
208. A method of treating joint inflammation in a patient in need thereof comprising administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.
- 25 209. A method of treating inflammatory bowel disease in a patient in need thereof comprising administering to said patient a pharmaceutically effective amount of a compound according to any one of claims 3 to 178.
- 30 210. A method of treating inflammatory bowel disease in a patient in need thereof comprising administering to said patient a pharmaceutically effective amount of a composition according to any one of claims 1, 2 or 179.
211. A process for preparing the compound of formula (I) according to claim 161, characterized in
35 that an acid of formula (D):



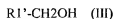
in which R1' has the meaning given in Claim 161 for R¹, in which the possible reactive functions are optionally protected with protecting groups,

is subjected to an esterification reaction to give an acid ester of formula (II)



5 in which R1' has the meaning given above and alk represents an alkyl radical,

is subjected to a reduction reaction to give the alcohol of formula (III):



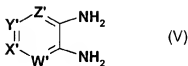
in which R1' has the meaning given above,

which is oxidized to the aldehyde of formula (IV):



in which R1' has the meaning given above,

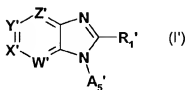
and the compound of formula (D) or compound of formula (IV) as defined above is reacted with a diamine of formula (V):



15

in which W', X', Y' and Z' have the meanings given in Claim 161, respectively, for W, X, Y and Z, in which the possible reactive functions are optionally protected with protecting groups,

20 to give a compound of formula (I'):



25 in which A5' has the meaning given in Claim 161 for A₅, in which the possible reactive functions are optionally protected with protecting groups, and R1', W', X', Y' and Z' have the meanings given above,

the compound of formula (I') being a compound which may be a compound of formula (I) and which, in order to obtain a compound or other compound of formula (I), may be subjected, if desired and if

30 necessary, to one or more of the following conversion reactions, in any order:

- a) an esterification reaction of an acid function,
 - b) a saponification reaction of an ester function to an acid function,
 - c) an oxidation reaction of an alkylthio group to the corresponding sulphoxide or sulphone,
 - 5 d) a reaction for conversion of a ketone function to an oxime function,
 - e) a reaction for reduction of the free or esterified carboxyl function to an alcohol function,
 - f) a reaction for conversion of the alkoxy function to a hydroxyl function, or alternatively of the hydroxyl function to an alkoxy function,
 - g) a reaction for oxidation of an alcohol function to an aldehyde, acid or ketone function,
 - 10 h) a reaction for conversion of a nitrile radical to a tetrazolyl,
 - i) a reaction for removal of the protecting groups that may be borne on the protected reactive functions,
 - j) a salification reaction with a mineral or organic acid or with a base to give the corresponding salt,
 - k) a reaction for resolution of the racemic forms into resolved products,
- 15 the said compound of formula (I) thus being obtained in any possible racemic, enantiomeric or diastereoisomeric isomer form.

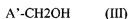
212. A process for preparing the compound of formula (I) according to claim 1, corresponding to formula (IA) according to any one of claims 165, 167 or 174, characterized in that an acid of formula
- 20 (D):



in which A' has the meaning given in any one of claims 165, 167 or 174 for A, in which the possible reactive functions are optionally protected with protecting groups, is subjected to an esterification reaction to give an acid ester of formula (II)

- 25 $A'-COOalk \quad (II)$

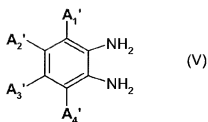
in which A' has the meaning given above and alk represents an alkyl radical, is subjected to a reduction reaction to give the alcohol of formula (III):



- in which A' has the meaning given above,
- 30 which is oxidized to the aldehyde of formula (IV):



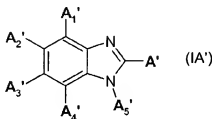
in which A' has the meaning given above, and the compound of formula (D) or compound of formula (IV) as defined above are reacted with a diamine of formula (V):



in which A₁' , A₂' , A₃' and A₄' have the meanings given in any one of claims 165, 167 or 174, respectively, for A₁, A₂, A₃ and A₄, in which the possible reactive functions are optionally protected

5 with protecting groups,

to give a compound of formula (IA'):



10

in which A₅' has the meaning given in any one of claims 165, 167 or 175 for A₅, in which the possible reactive functions are optionally protected with protecting groups, and A₁' , A₂' , A₃' and A₄' have the meanings given above,

the compound of formula (IA') is a compound which may be a compound of formula (IA) and which,
 15 in order to obtain a compound or another compound of formula (IA), may be subjected, if desired and if necessary, in any order, to one or more of the conversion reactions chosen from among the reactions a) to k) defined in Claim 211,

the said compound of formula (IA) thus obtained being in any possible racemic, enantiomeric or diastereoisomeric isomer form.

20

213. As medicinal compounds, the compounds of formula (I) as defined in any one of Claims 161 to 178, and also the addition salts with pharmaceutically acceptable mineral and organic acids or with pharmaceutically acceptable mineral and organic bases of the said compounds of formula (I).

25 214. As medicinal compounds, the compounds of formula (I) as defined in any one of Claims 156 to 159, and also the addition salts with pharmaceutically acceptable mineral and organic acids or with pharmaceutically acceptable mineral and organic bases of the said compounds of formula (I).

215. Pharmaceutical compositions containing, as active principle, at least one of the compounds of formula (I) as defined in any one of claims 156 to 159 or claims 161 to 178, or a pharmaceutically acceptable salt of this product or a prodrug of this compound and a pharmaceutically acceptable support.
216. Use of the compounds of formula (I) as defined in any one of claims 156 to 159 or claims 161 to 178, or of pharmaceutically acceptable salts of these compounds, for the preparation of a medicinal product intended for inhibiting the activity of a kinase protein.
217. Use of a compound of formula (I) as defined in any one of claims 156 to 159 or claims 161 to 178, for the preparation of a medicinal product for treating or preventing a disease characterized by deregulation of the activity of a kinase protein.
218. Use according to claim 216, in which the kinase protein is a tyrosine kinase protein.
219. Use as defined in claim 216, in which the kinase protein is chosen from the following group: FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, flt-1, IGF-1R, KDR, PDGFR, tie2 and VEGFR.
220. Use as defined in claim 216, in which the kinase protein is KDR.
221. Use as defined in Claim 216, in which the kinase protein is tie2.
222. Use as defined in Claim 216, in which the kinase protein is in a cell culture.
223. Use as defined in Claim 216, in which the kinase protein is in a mammal.
224. Use of a compound of formula (I) as defined in any one of claims 156 to 159 or claims 161 to 178, for the preparation of a medicinal product for treating or preventing a disease chosen from the following group: disorders of the proliferation of blood vessels, fibrotic disorders, disorders of the proliferation of "mesangial" cells, metabolic disorders, allergies, asthma, thrombosis, diseases of the nervous system, retinopathy, psoriasis, rheumatoid arthritis, diabetes, muscle degeneration and cancers.
225. Use of a product of formula (I) as defined in any one of claims 156 to 159 or claims 161 to 178, for the preparation of a medicinal product for treating or preventing a disease chosen from the following group: disorders of the proliferation of blood vessels, fibrotic disorders, disorders of the

proliferation of "mesangial" cells, retinopathy, psoriasis, rheumatoid arthritis, diabetes, muscle degeneration and cancers.

226. Use of a compound of formula (I) as defined in any one of claims 156 to 159 or claims 161 to 178, for the preparation of a medicinal product for preventing or treating diseases associated with an uncontrolled angiogenesis.
227. Use of a compound of formula (I) as defined in any one of claims 156 to 159 or claims 161 to 178, for the preparation of a medicinal product for treating diseases in oncology.
228. Use of a compound of formula (I) as defined in any one of claims 156 to 159 or claims 161 to 178, for the preparation of a medicinal product for treating cancers.
229. Use according to claim 227, for the treatment of solid tumours.
230. Use according to Claim 228 or 229, for the treatment of cancers that are resistant to cytotoxic agents.
231. Use according to claim 228 or 229, for the treatment of breast cancer, stomach cancer, cancer of the ovaries, cancer of the colon, lung cancer, brain cancer, cancer of the larynx, cancer of the lymphatic system, cancer of the genito-urinary tract including the bladder and the prostate, bone cancer and cancer of the pancreas.
232. Use according to claim 228 or 229, for the treatment of breast cancer, cancer of the colon or lung cancer.
233. Use of the compounds of formula (I) as defined in claims 156 to 159 or claims 161 to 178, for the preparation of medicinal products intended for cancer chemotherapy.
234. Use of the compounds of formula (I) as defined in claims 156 to 159 or claims 161 to 178, for the preparation of medicinal products intended for cancer chemotherapy alone or in combination.
235. Compounds of formula (I) as defined in any one of claims 156 to 159 or claims 161 to 178, as kinase inhibitors.

236. Compounds of formula (I) as defined in any one of claims 156 to 159 or claims 161 to 178, as KDR inhibitors.

237. Compounds of formula (I) as defined in any one of claims 156 to 159 or claims 161 to 178, as
5 tie2 inhibitors.

238. A method according to claim 190 or claim 191 wherein the cancer being treated is breast cancer, stomach cancer, cancer of the ovaries, cancer of the colon, lung cancer, brain cancer, cancer of the larynx, cancer of the lymphatic system, cancer of the genito-urinary tract, bladder, prostate, bone
10 cancer or cancer of the pancreas.

INTERNATIONAL SEARCH REPORT

 International Application No.
 PCT/GB 02/04763

A. CLASSIFICATION OF SUBJECT MATTER

 IPC 7 A61K31/4184 C07D403/04 C07D403/14 C07D413/04 C07D413/14
 C07D405/14 C07D409/14 C07D491/04 C07D401/14 C07D487/04
 C07D471/04 A61P35/00 //(C07D491/04, 319:00, 235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 53268 A (AGOURON PHARMACEUTICALS, INC.) 26 July 2001 (2001-07-26) the whole document ---	1-238
X	WO 01 02369 A (AGOURON PHARMACEUTICALS, INC) 11 January 2001 (2001-01-11) the whole document ---	1-238
X	WO 01 00610 A (AVENTIS PHARMA DEUTSCHLAND GMBH) 4 January 2001 (2001-01-04) the whole document ---	1-238
X	EP 1 006 114 A (GRELAN PHARMACEUTICAL CO., LTD.) 7 June 2000 (2000-06-07) the whole document --- -/--	1-238

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"S" document member of the same patent family

Date of the actual completion of the international search

10 February 2003

Date of mailing of the international search report

20/02/2003

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	DE 22 63 878 A (CIBA-GEIGY AG) 5 July 1973 (1973-07-05) * le document en entier, en particulier composés 19-26 * ---	1-238
X	DE 21 30 030 A (BAYER AG) 21 December 1972 (1972-12-21) the whole document ---	1-238
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X	SINGH S P ET AL: "Formation and dehydration of a series of 5-hydroxy-5-trifluoromethyl- 4,5-dihydropyrazoles" JOURNAL OF FLUORINE CHEMISTRY, vol. 94, no. 2, 5 April 1999 (1999-04-05), pages 199-203, XP004163162 the whole document ---	1-238
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>TAGAKI K ET AL: "Synthesis of pyrimidino'4,5-b'1,5!benzodiazepin-2-ones and pyrimidino'1,6-a!benzimidazol-1-ones from 4-ethoxycarbonylamino-1H-1,5-benzodiazepine-3-carbonitrile via 4-(2-aminoanilino)pyrimidin-2(1H)-one-5-carbonitriles"</p> <p>JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 23, no. 5, 1986, pages 1443-1449, XP002204299</p> <p>the whole document</p> <p>---</p>	1-238
X	<p>SENGA K ET AL: "Synthesis of pyrazolo'1',5':1,2!-1,3,5-triazino'5,6-a!benzimidazoles"</p> <p>JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 12, no. 5, October 1975 (1975-10), pages 899-901, XP002204300</p> <p>the whole document</p> <p>---</p>	1-238
X	<p>FINAR I L ET AL: "The preparation and some reactions of 4-formyl-1-phenyl-pyrazoles"</p> <p>JOURNAL OF THE CHEMICAL SOCIETY, 1961, pages 2733-2738, XP002204301</p> <p>the whole document</p> <p>---</p>	1-238
X	<p>DATABASE CAPLUS 'Online!</p> <p>CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;</p> <p>Database accession no. 1995:505008</p> <p>XP002204302</p> <p>RN 109073-55-4</p> <p>& J. INDIAN CHEM. SOC.,</p> <p>vol. 70, no. 11-12, 1993, pages 1035-1042,</p> <p>---</p>	1-238
X	<p>DATABASE CAPLUS 'Online!</p> <p>CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;</p> <p>Database accession no. 1975:97992</p> <p>XP002204303</p> <p>RN 55548-52-3</p> <p>& KHIM. GETEROTSIKL. SOEDIN.,</p> <p>no. 12, 1974, pages 1690-1694,</p> <p>---</p>	1-238
X	<p>DATABASE CAPLUS 'Online!</p> <p>CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;</p> <p>Database accession no. 1994:605262</p> <p>XP002204304</p> <p>rn 157946-31-1, 157946-32-2, 157946-33-3, 157946-34-4, 157046-35-5</p> <p>& J. CHEM. RES., SYNOP.,</p> <p>no. 7, 1994, pages 286-287,</p> <p>---</p> <p>-/--</p>	1-238

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
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E	WO 03 004488 A (CHIRON CORPORATION) 16 January 2003 (2003-01-16) the whole document -----	1-238

INTERNATIONAL SEARCH REPORT

international application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 180-210 and 238 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

Claims Nos.: 1-3, 5-8, 10-13, 143, 161-167, 173-175, 179-213, 215-238
(all in part)

Present claims 1-3, 5-8, 10-13, 143, 161-167, 173-175, and implicitly 179-213, 215-238 relate to an extremely large number of possible compositions and compounds, and their use. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and compositions claimed.

Furthermore, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

In the present case, the claims so lack novelty and/or support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently a complete search has only been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claims 4, 9, 14-142, 168-172, 176-178, their compositions and their use.

The numbering and/or wording of certain claims is so unclear (see e.g. claims 48, 104 and 127) that a precise reference of the cited documents to the claims is impossible.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

 International Application No
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INTERNATIONAL SEARCH REPORT

Original Application No

PCT/GB 02/04763

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